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Discovery and Information Use Patterns of Nobel Laureates in Physiology or Medicine

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Discovery and Information Use Patterns of Nobel Laureates in Physiology or Medicine

by

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Dedication

I dedicate this dissertation to my first teachers: my father, George Sheldon Balcom, who passed away before this task was begun, and to my mother, Marian Dyer Balcom, who passed away before it was completed. I also dedicate it to my dissertation committee members: Drs. Billie Grace Herring, Brooke Sheldon, Julie Hallmark and to my supervisor, Dr. Glynn Harmon. They were all teachers, mentors, and friends who lifted me up when I was down.

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I benefited from studying under Drs. Julie Hallmark, Billie Grace Herring and Glynn Harmon in the early 1970s in the Master's program at The Graduate School of Library Science (now The School of Information) at The University of Texas at Austin. I wanted an opportunity to work with them again, and enrolled in the Ph.D. program in the early 1990s. Dr. Brooke Sheldon came to Austin to assume the School's Deanship shortly after I returned, and I soon looked upon her presence as a strong bonus. This project has

taken a long and winding road over extended duration. Professors Herring and Hallmark retired from their positions at The University during the course of this journey. I asked both of them to remain on my committee during their retirement, and I was pleased and grateful that both agreed to my request and graciously contributed their time during retirement. Dean Brooke Sheldon left to assume another Dean's position at The University of Arizona. She also agreed to continue on my committee and continued to mentor and encourage me during her heavy administrative schedule, and subsequently when she retired.

This dissertation would not have been possible without the close mentoring of Dr. Glynn Harmon. His book, *Human Memory and Knowledge* (1973), provided the initial inspiration for the investigation of scientific discoveries. I owe him a special debt of gratitude for suggesting that the lectures were probably organized in about seven chunks or units per lecture; that I try to reanalyze the pilot cases using the systems levels and 20 critical subsystem categories from J. G. Miller's *Living Systems* (1995); and that a discovery template could be developed from that ontology to guide future research.

The faculty of The School of Information has granted me several extensions beyond the normal time limit for a dissertation so that I could complete this investigative journey; I thank them for their patience and support. Also, I wish to thank the staff of The School of Information, especially Carol Carreon, Melba Claymon, and Kathleen Adrian, for the prompt, caring, professional support they gave to me and constantly give to all iSchool students.

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This study was also possible because The Nobel Foundation decided in the 1960s to make the Laureates' lectures available to the public. Elsevier Publishing Company published the first four volumes covering the period from 1901 to 1970. Although the original four volumes went out-of-print, The Foundation permitted World Scientific Publishing Company to continue to the *Nobel Lectures* series and, finally, to reprint those out-of-print volumes both in hardcopy and CD-ROM. In addition, The Foundation recently made the lectures and a wealth of other information available on its web site (http://www.nobel.se/), thus benefiting students at virtually all levels of education.

Much of this dissertation was based on the monumental work by James Grier Miller, M.D., Ph.D., *Living Systems*. I am indebted to him and the McGraw-Hill Publishing Company for publishing his book in 1978. I am grateful that the University Press of Colorado reprinted it in a 1995 paperback edition with the significant addition of Dr. Miller's "Preface to the Paperback Edition." That preface assumed a prominent place in this study.

Finally, I wish to thank my husband, James L. Garrison, for his patience during this odyssey; for frequently helping care for my mother when I was out of town; for taking care of our home, including our pet cats; and for helping load and unload my research materials, luggage, and computer countless times.

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Discovery and Information Use Patterns of Nobel Laureates in Physiology or Medicine

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This investigation identifies and formalizes patterns of discovery among Nobel Laureates in physiology or medicine. The main hypothesis is that discovery patterns are characterized by the gradual acquisition of critical, unorganized masses of findings that, when abstracted and ordered, produce a discovery outcome. Discoveries tend to consist of approximately seven plus or minus two basic components, which reflect the cognitive limits of short-term or working memory. The second hypothesis is that critical research incidents, such as unanticipated problems or flashes of insight, affect individual research progress. The third hypothesis is that Laureate physicians employ clinical problem-solving heuristics to guide their research. Content analysis of 20 Nobel Laureate autobiographical research accounts and statistical analysis of 62 accounts, all published by the Nobel Foundation between 1901 and 1990, were performed.

A systems model emerged early in the analysis as a dominant feature of discovery, and clearly suggested the use of General Systems Theory ontology (Miller, J. G., *Living Systems*) to formalize the nature of the discoveries and demonstrate the

important role of human short-term memory limitations in knowledge synthesis. A sub-sample analysis of five early and five recent Laureate discoveries describes subsystems that closely match Miller's systems template. Further analysis of 62 Laureate discovery accounts reveals an average of seven sections per account (Mean=7.1; *SD*=2.84; *CI*=95%), while a *t*-test reveals no significant difference between an actual mean of 7.1 and a hypothetical mean of 7.0 (*t*=0.2685; *df*=61 and Mean=7.1; *DF*=2.84; *CI*=95%). The General Systems discovery ontology, with its eight to ten unique subsystems, also reflects short-term memory limitations of seven plus two chunks and helps to explain past discovery patterns.

The analysis supports the first hypothesis but only partially supports the second and third hypotheses. Laureates relied on systems models to conduct their research and represent their discoveries. Critical incidents and clinical problem-solving heuristics played a relatively minor role in progress toward discovery. The General Systems ontology could be developed into a "discovery template" to support future discovery efforts.

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Chapter 1: Introduction: Learning From the Scientific Discovery Process

OVERVIEW

This investigation seeks to analyze a broad range of cases of individual Nobel Laureate autobiographical accounts of scientific discoveries in medicine and physiology. The investigation's purpose is to detect patterns of scientific discovery and the concomitant information seeking processes.

Nobel Laureates are clearly regarded as masters of research in their respective areas, yet there have been very few studies of their discovery and information use patterns despite the widespread availability of published, autobiographical accounts of their research. Such patterns have the potential of revealing common as well as unique approaches and methods used to solve fundamental research problems. In turn, the successful isolation of such patterns holds promise for the direct improvement of attacks on future research problems, including the improvement of information systems to support fundamental research. Additionally, these discovery patterns provide a context for the study of how master researchers actually use recorded knowledge and that of colleagues, and transmit their own knowledge to others.

To study discovery and information use patterns, this investigation employs autobiographical accounts of Nobel Laureate discoveries published by the Nobel Foundation, the characteristics of which are explained below. The basic analytical method employed to study the written text of these autobiographical accounts is *content analysis,* with an emphasis on the *critical incident* method. These analytical methods are

defined below and explained more fully in the Research Approach and Case Analysis Method section of this chapter.

Content Analysis involves the use of general and specific analytical concepts or categories in the rigorous analysis of written text for the purpose of identifying and recording meaningful explicit and implicit themes, events, relationships, anomalies, patterns, and the like.

Critical Incidents are those events that occur in the course of research efforts that appear to be influential in framing and deciding research outcomes. Critical incidents include events such as those which lead to the initiation of research or those that are apparently instrumental in hindering, assisting, redirecting or culminating the research effort. Here, the use of critical incident analysis is regarded as a specific form of content analysis.

THE NOBEL PRIZE

December 10, 1996, marked the 100th anniversary of the death of Alfred Bernhard Nobel, the inventor of dynamite whose most enduring legacy has been the Prizes which he established through a bequest in his will, (Feldman, 2000; Harittai, 2002; Levinovitz & Ringertz, 2001, *Nobel lectures, including presentation speeches and laureates' biographies: Physiology or medicine, 1901-1921*). One of the three Nobel Prizes devoted to the sciences is in the area of physiology or medicine (Appendix A). Other Nobel Prizes are awarded in the areas of chemistry and physics. Conferral of this highly respected Prize is an indication of completing preeminent research and producing knowledge of benefit to all mankind. Consequently, the Nobel Laureates constitute a group of elite scientists who are generally regarded as expert researchers in their specialties, as well as exemplars in biomedical research.

Such scientists do better work than others and make more important discoveries. It seems reasonable to presume that the superior scientists have more effective methodological principles and problem-solving methods, are better able to recognize critical features in data and theoretical formulations, and have better laboratory and computing instruments and are more skillful in the laboratory than their less successful colleagues (Langley *et al.*, 1987, pp. 45-46).

Despite the availability of recorded and detailed accounts of Nobel Laureate research since 1901, information scientists have generally neglected the study of discovery and information use patterns of this elite group. Knowledge of how these experts work can provide valuable insights into the design of computer-based research support systems that would facilitate scientific collaboration and communication, publication and dissemination, the development of network search engines and agents, or the discovery process itself.

Since the start of the twentieth century, autobiographical accounts from each Nobel Laureate or group of Nobel Laureates in Physiology or Medicine have, with a few exceptions, been published each year. These accounts provide relatively complete, rigorous and detailed reconstructions of each research effort. The reconstructions include several kinds of data: citations or references to pioneers and other colleagues to whom the Laureate is intellectually indebted; the evolution of the Laureate's research strategy as problems and experiments were defined and redefined; the development of initial, intermediate and concluding hypotheses; accidental and serendipitous research events; telling statements worthy of quotation that reveal unusual insights regarding the scientist's area of interest or the enterprise of science itself; the framing, organization and presentation of discoveries; citations to the Laureate's own publications, which reveal the importance of publication as a means of summarizing and organizing findings, filling

their own cognitive needs, and establishing the ownership of ideas; the careful verification of results for purpose of scientific replication; and finally, attempts to generalize findings beyond verified hypotheses and to discuss their overall significance.

Nobel Laureate autobiographical accounts are published annually in *Les Prix Nobel* as acceptance speeches given at annual award ceremonies before the King and Queen of Sweden. In addition, these accounts have been translated into English, and compiled and published in eight volumes, starting with *Nobel Lectures, Including Presentation Speeches and Laureates' Biographies: Physiology or Medicine, 1901-1921* (*Nobel lectures, including presentation speeches and laureates' biographies: Physiology or medicine, 1901-1921*, 1967). Additional compilations are published in subsequent volumes having the same title which cover the years 1922-1941 (*Nobel lectures, including presentation speeches and laureates' biographies: Physiology or medicine, 1922-1941*, 1965), 1942-1962 (*Nobel lectures, including presentation speeches and laureates' biographies: Physiology or medicine, 1942-1962*, 1964), 1963-1970 (*Nobel lectures, including presentation speeches and laureates' biographies: Physiology or medicine, 1963-1970*, 1972), 1971-1980 (*Nobel lectures, including presentation speeches and laureates' biographies: Physiology or medicine, 1971-1980*, 1992), 1981-1990 (*Nobel lectures, including presentation speeches and laureates' biographies: Physiology or medicine, 1981-1990*, 1993), 1991-1995, and 1996-2000.

RATIONALE AND APPROACH

Because the autobiographical accounts are lengthy, detailed, and rigorously explained they can well serve as rich repositories of primary data. While Nobel Laureates can obviously incorporate their own reporting distortions, explanatory gaps and biases into the autobiographical accounts of their own discoveries, this investigator has found their accounts to be generally well documented and quite rigorously factual. Additionally,

other scientists confirm the replicability of their results. This study examines the primary data through general content analyses of the aforementioned Nobel Laureate lectures. The content of these lectures also occasionally reveals the occurrence of various kinds of critical incidents--those events that had a significant influence in impeding, redirecting, or accelerating research efforts, or even reorganizing the ideas that drove and focused research.

As a result of pilot studies, it was observed that many, if not most, Nobel Laureates were educated as physicians. They have tended to use the patterns of *clinical problem solving* and *consultation* with colleagues that they learned in medical school and practiced in clinical settings. The nature of clinical problem-solving and collegial consultation has been investigated and explained in key works in medical informatics (Cutler, 1985; Weed, 1991). Laureates also cite or reference the work of their predecessors and contemporary colleagues. These citations are briefly analyzed in this study. The methods used are more fully explained in the Research Approach and Case Analysis Method section below.

Critical research incidents are of interest in this investigation, insofar as they can reveal which research functions might be augmented by a research support system. Examples of critical incidents typically encountered during the course of Nobel Laureate research include: stoppage of research owing to a lack of information or the need for a new laboratory technique or instrument; the redirection or refocusing of research based on new insights or findings; the revision or adoption of hypotheses; failure to produce or draw upon published findings; going against the prevailing model or theory that had driven past research on the same topic; unexpected observations or findings; or decisive evidence about the basis of key physiological or biochemical mechanisms.

The need for analysis of fundamental research and information use patterns is apparent in several ways. First, in light of what some scholars have regarded as a long-term impasse in information retrieval research, including its neglect of fundamental research support, Weed (1991) asserted that the cognitive load on the average medical doctor is extreme and that computer-based enhanced cognition is essential to professional problem solving. The same statement can be made for scientists in fundamental research, who find it increasingly difficult to stay abreast of new developments in their fields. Cognitive and artificial intelligence studies of problem solving have demonstrated that depth of knowledge in problem domains is crucial to success. Human experts, such as grandmasters in chess or Nobel Laureates, have acquired from 50,000 to 100,000 chunks of heuristic problem-solving information related to their subject during the course of their education and experience (P. Harmon & King, 1985; Langley et al., 1987). A chunk may be defined as "a familiar collection of more elementary units that have been interassociated and stored in memory repeatedly and that act as a coherent, integrated group when retrieved" (Tulving & Craik, 2000, p.12)

Second, the emergence of Web and network-based research appears to demand a reexamination of how research is, or should be, conducted (Lindberg & Humphreys, 1995, "U.S. Plans for virtual laboratories by Internet", 1996). As early as 1993, Taubes noted that computer-mediated communication via the Internet was already changing the way scientists interact to facilitate knowledge synthesis. By 1995 Internet communications involved consultations among physicians and scientists in 18 countries who were trying to diagnose the cause of a serious illness in a Beijing University graduate student (Gunby, 1995). Today, Web-augmented research is almost universally common. While computer-mediated communication has enhanced knowledge synthesis, the corresponding complexities of network environments can add to user cognitive loads.

Fortunately, there are numerous efforts to bring order to the rapidly growing information jungle, including the development of research engines.

A third need concerns the development and implementation of autonomous, intelligent agents, that is, computer programs that can pursue internal goals by receiving information from a perceived environment and making rational decisions ("Software agent," 2005) that would locate information, negotiate with other agents for use of the information, and deliver it to the agent's owner. Agent software could also ease cognitive loads by providing consistent intelligent interfaces to information systems and services. The successful isolation of Nobel Laureate discovery and information use patterns should provide insight into the future development of heuristics for the scientists themselves and for search engines, intelligent intermediaries, and agents.

PROBLEM AND PURPOSE: THE EXPLORATION OF DISCOVERY DYNAMICS AND KNOWLEDGE SYNTHESIS

As stated above, the detection of the dynamics and patterns of the fundamental research process and its underlying base of intellectual linkages can be revealing for a number of purposes. First, the successful detection of research and discovery dynamics and mechanisms can alter the conduct of future research. Second, such studies can reveal how successful scientists inform their relevant sets of colleagues as well as how they draw in and incorporate the findings of others. Thus, such efforts appear to hold promise as a genré of information need and use study that, in turn, can provide a more realistic basis for the redesign of information access and knowledge production systems. Third, such studies can illustrate the rather frequent but generally overlooked incidence and role of various "anomalies" in research, including serendipity, fortuitous accidents, spontaneous insights, and the aesthetic motivations of scientists.

This investigation, then, attacks the problem of identifying common research strategies, patterns, and the underlying information usage dynamics, among a number of Nobel Laureate discoveries. Accordingly, the purposes of this investigation are three-fold:

1. to explore the dynamics and patterns of discovery of Nobel Laureates in Physiology or Medicine as revealed by the official autobiographical accounts of the Nobel Laureates themselves in their acceptance speeches. This exploration includes the manner in which the Laureates assimilate and organize knowledge during the course of their research;
2. to identify critical incidents which had a significant impact on the Laureate's research outcomes. As stated earlier, these events, often subtle in their appearance and influence, serve to mark those points at which the Laureate's research is inhibited or stopped, catalyzed or accelerated, or redirected to more fruitful lines of inquiry. Typically, these critical incidents serve to illustrate needs for information, as well as needs to summarize and publish findings, and to stake claims to these findings;
3. to identify the nature of knowledge synthesis that underlies Laureate research pursuit. Knowledge synthesis involves Laureate authoring and reporting efforts, use of medical problem-solving methods, informal consultations with colleagues, and formal acknowledgements of colleagues. Knowledge synthesis involves filtering, integrating, and interpreting research findings; narrowing the attack on research problems; incorporating experimental methodology; and cross-checking, organizing and generalizing findings.

Additionally, the study briefly discusses implications for the future design of information systems that will serve to support or direct fundamental research in medicine and physiology. As early as the mid-1990s it was noted that contemporary science finds itself entering an era when an increasing amount of research, including simulations and experiments, will be conducted via Web-based search and collaboration. It therefore appears to be vital to sketch parameters for intelligent agents or search engines specifically adapted to the requirements of fundamental research (Lindberg & Humphreys, 1995, "U.S. Plans for virtual laboratories by Internet", 1996; Ward, 1995; Weld *et al.*, 1995).

NOBEL LAUREATE RESEARCH: RELATED EXPLORATIONS

A number of studies have directly or indirectly explored the general nature of fundamental scientific research for empirical and normative purposes. Such quests tended to pursue the objective of explaining how discoveries or breakthroughs were made, and to synthesize the lessons applicable to future efforts. Some of these studies emerged from the general history or sociology of science. Others studied the information need and use patterns of scientists, including such topics as creativity and other aspects of cognitive functioning. Numerous studies attempted to lay the groundwork for the computerization of research support. A few of these studies concentrated specifically on the scrutiny of Nobel Laureate discoveries.

In *The History of Science and the New Humanism*, Sarton described scientific progress as being analogous to climbing the steps of a staircase, wherein each step serves as a platform to reach the next step:

> Indeed the scientific activity is the only one which is obviously and undoubtedly cumulative and progressive…. When one investigates carefully the genesis of any discovery, one finds that it was gradually prepared by a number of smaller ones, and the deeper one's investigation, the more intermediary stages are found. Our

> first impression of scientific progress is like that of gigantic stairs, each enormous step representing one of those essential discoveries which brought mankind almost suddenly up to a higher level, but that impression is imperceptibly obliterated as we pursue our analysis. The big steps are broken into smaller ones, and these into others still smaller, until the steps seem to vanish altogether—yet they never vanish (Sarton, 1988).

Price (1961, 1963) likewise provided models of scientific growth that illustrated its cumulative and progressive nature. His seminal work provided crude measures of the rate of scientific growth and the relative sizes of various scientific fields.

Simon and associates studied scientific discovery and problem solving from artificial intelligence perspectives. Similarly, they viewed progress in science as a step-by-step progression, wherein the achievement of each step is driven by the data gathered. This process subsequently feeds into and directs progress to the next step:

> The scientific enterprise is dedicated to the extension of knowledge about the external world. It is usually conceived as being made up of four main kinds of interrelated activities: gathering data, finding parsimonious descriptions of the data, formulating explanatory theories, and testing the theories. Sometimes the second category (description) and third (explanation) are merged. Usually these activities are conceived as occurring in a cyclical fashion. Theories are formulated, predictions are made from them, data are gathered, and the theories are tested by confronting their predictions with the data. Failure of data to support theories leads, in turn, to formulation of new theories (Langley et al., 1987, pp. 18-19).

This view is still widely accepted. Earlier, however, sociologist Thomas Kuhn (1962) published his theory of scientific revolution, which held that it was only normal scientific progress that relied on a cumulative process in which scientific work proceeds within a generally accepted theory or framework. Kuhn asserted that real scientific progress, progress which expands the scientific frontier, is not the result of accumulation. Rather, Kuhn argued that the typical scientist is conservative and tends to be a conformist. The research of a typical scientist focuses on problems that confirm and extend the predominant framework favored by the majority of colleagues in his or her

field. For progress to occur, a rebel scientist—usually young and not fully indoctrinated with the field's generally accepted theory—recognizes the inadequacies of the old theory and abandons it to develop a totally new one. Eventually, a significant number of typical scientists will adopt the new theory and the revolution will then be complete.

The interpretations by Sarton, Price, Simon, and Kuhn are, however, based on broad and rather philosophical analyses of scientific development, rather than rigorous case-by-case analysis. Harmon (1973) provided case studies of a number of scientific discoveries, including those of a few Nobel Laureates. These case studies revealed that, given the accumulation of a chronological series of about seven major scientific contributions on the same problem, some sort of integration or synthesis must occur, otherwise, progress on the problem grinds to a halt for the want of structuring. The synthesis must occur because the accumulated knowledge supersedes cognitive manageability, which is governed largely by the limits of human short-term memory. The limits of short-term memory were statistically demonstrated in the seminal article by G. A. Miller (1956), "The Magic Number Seven Plus or Minus Two." Thus, about seven cognitive elements or chunks make up the key components of a scientific discovery. Once a discovery occurs, science turns to "mopping up" operations to fill knowledge gaps and establish the validity of the discovery. Because each discovery tends to raise more questions than it answers, the discovery provides a foundation for subsequent scientific revolution. Accordingly, the above cumulative models of Sarton, Simon and Price need not contradict Kuhn's revolutionary model. Knowledge accumulation, it seems, similarly occurs in the process of scientific revolution.

Harmon (1973) also presented a formula which makes possible either the prediction or retrodiction of discoveries through case-by-case analysis. Given the first two or three major contributions, this formula is able to predict a probable year of

discovery. A more elaborate mathematical approach to case analysis and the prediction of scientific discoveries in the field of logic was published in the journal *Nature* (Goffman & Harmon, 1971). Thus, the systematic analysis of Nobel Laureate accounts on a case-by-case basis appears to be a relatively fruitful approach to the detection of discovery dynamics and information use. The analysis of each case can reveal the characteristics of knowledge accumulation in each discovery pattern and the limiting impact of human short-term memory in the discovery process. To achieve cognitive manageability, short-term memory limitations require scientists to limit the number of items they analyze at any given time to about five to nine key representations.

Harriet Zuckerman conducted a sociological study of Nobel Laureates in the sciences for her doctoral dissertation and subsequent studies summarized in her book, *The Scientific Elite: Nobel Laureates in the United States* (1977). Although her work includes a citation analysis of the Laureates' publications, Zuckerman tells us little about discovery patterns or how the Laureates themselves conduct research.

A relatively high proportion of information need and use studies have addressed the nature of scientific and engineering research and information needs, but few have focused on the process of discovery. Early on, Menzel, (1966) lamented the paucity of well-planned and executed information use studies, especially in science information. An *Annual Review of Information Science and Technology* article by Lin and Garvey (1972) on "Information Needs and Uses" covered a greater amount of literature, but the enduring question of how to best serve the information needs of scientists remained. Griffith, Jahn, and Miller (1971) examined informal communication in science and suggested that informal contacts are frequent but somewhat random. Studies by Bernard, Shilling, and Tyson (1963, 1964) surveyed bio-scientists in 64 laboratories. Through questionnaires, these scientists were queried about all communication channels that were influential in

their most recent research. Their studies revealed that scanning and reading literature is one and a half times as important to these researchers as discussions at meetings or in their home laboratories. This same study also attempted to measure the success and productivity of the laboratories. Included under a category termed "information efficiency" is the frequency of reports of "lucky accidents" from informal communication.

A more recent study by Hallmark (1994) involved scientists primarily in academic institutions in the areas of chemistry, biology, mathematics, physics, and geology. Hallmark used a methodology similar to that employed by King (1979) in his study of scientific communication, and identified scientists who had recently published in key journals. These scientists were then queried to determine how they first became aware of a particular article they cited and how they actually obtained a copy of that article. While this study again underscored the differences in information access and use between various disciplines, a more significant finding is that these scientists shared a feeling that they are increasingly isolated from their journal literature and that literature is increasingly inaccessible notwithstanding present or future electronic innovations in information storage and retrieval.

Another form of information need and use study method is content analysis, which focuses on the scrutinizing of any kind of written text to discern manifest and latent content. Case (2002, pp. 210-211) noted that content analysis has been successfully applied in numerous areas, including medicine. Content analysis can be deployed to detect the research patterns in the writings of scientists and their portrayal of hypothesis formation and synthesis of experimental data. Nevertheless, information need and use studies seldom address the scientific discovery process itself. Content analysis might be profitably applied to historical accounts of discoveries. Because Nobel Laureate accounts

are indeed autobiographical historical accounts, and serve as a key form of primary evidence, these accounts appear to be particularly suitable for content analysis.

Menzel reviewed the use of critical incident technique, a form of content analysis, to study information need and use in the first volume of the *Annual Review of Information Science and Technology* (1966). That technique again merited citation by Hewins in her (1990) review of information-need-and-use studies for the *Annual Review*. Both Menzel and Hewins reviewed Allen's MIT study of information needs and use by scientists in a research and development setting and the development of a "Solution Development Record" which was devised to record critical research incidents and to link decision making with information intakes (Allen, 1966). Hewins also reviewed a project at the National Library of Medicine (NLM), which utilized critical incident technique to study the behavior of MEDLINE users. The NLM study interviewed the users regarding the "critical" incident, which prompted the MEDLINE search. Three categories were defined and arranged hierarchically: (1) the need that prompted the search, (2) the use of information obtained with respect to patient-care decisions, and (3) the final outcome of the decision made. Within each, a taxonomy of categories was constructed from the users' answers.

Such studies, however, did not go very far in revealing the deeper dynamics of research and discovery. Instead, they focused on sociological patterns, the roles of information gatekeepers, and the use of various types of literature. Early studies on information need and use focused on specific settings, and thus suffered from a lack of generalizability, tended to be poorly controlled, and tended to be atheoretical (Dervin & Nilan, 1986; Herner & Herner, 1967; Lin & Garvey, 1972; Menzel, 1966; Paisley, 1968). Many of these limitations prevail to the present day.

The cognitive science movement has served to compensate somewhat for the methodological and theoretical weaknesses of the information-need-and-use movement. Cognitive science focuses, among other things, on the more rigorous study of the nature of the mind, the psychological dynamics of problem solving and inquiry, the synergistics of mind and computer, and more recently, artificial intelligence (Gardner, 1987; Luger, 1994; Von Eckardt, 1993). The cognitive science movement is based partially on the rationalist view of knowledge genesis and use. Rationalism asserts that knowledge is largely innate, and that the mind's pre-existing cognitive structures provide for language syntax, the mediation and mappings of sensory and experiential data, and the ordering of behavior. In contrast, the empiricist view, a favored working assumption of normal information science, holds that data derive from external sources, such as books, journals, and computer displays (Gardner, 1987). The rationalist perspective of information use points directly to the need to investigate the nature of cognitive mechanisms and intellectual linkages that actually stimulate and catalyze scientific discovery. For Nobel Laureates, such rationalist factors as creative research environments, the aesthetics of research experience, and the process of organizing, authoring and publishing, all appear to be as crucial to productivity as "taking in" empirical data from predecessors or other colleagues, as illustrated by this quotation:

> The study of biology is partly an exercise in natural esthetics. We derive much of our pleasure as biologists from the continuing realization of how economical, elegant and intelligent are the accidents of evolution that have been maintained by selection. A virologist is among the luckiest of biologists because he can see his chosen pet down to the details of all of its molecules (Baltimore, 1992, p. 215).

The presentation speeches, which introduce the scientists and their work to the assembly gathered to see them honored with the Nobel Prize, frequently provide insight into the scientific milieu:

> The constellation was promising: one physicist, Delbruck, one physician, Luria, and one biochemist, Hershey. With their different backgrounds and approaches they were able to launch truly concentric attacks on the fundamental problems. They worked independently but in close contact. Early on they formed their own school and the stimulating intellectual climate they created attracted talented scientists from many different fields with many different attitudes (Gard, 1972, p. 401).

Some cognitive science studies are more directly related to the study of discovery and knowledge synthesis and serve to support the rationalist view. For example, Ballesteros (1995) provided experimental evidence that unconscious thought processes, those which reside beyond a researcher's immediate realm of awareness, play a key role in the formulation of appropriate research questions. Because up to about 85% of human cognition resides in the unconscious realm, study of the role of unconscious processing in the conduct of research appears to be quite necessary, despite its implicit nature. In a related study, Erdelez pointed out the value of inadvertent but useful user information encounters. Her research indicated that some individuals are more attuned than others to locating information through this type of experience. She defined *information encountering* as:

> …the memorable experience of an unexpected discovery of useful or interesting information in the context of both information-related and non-information-related activities. The unexpected aspects of information encountering involve both the accidental discovery of information that had not been sought and the discovery of unforeseen characteristics of information that had been sought (Erdelez, 1995, p. 146).

Science tends to be something of a mystery to most lay persons, but some scientific discoveries are clearly more intriguing and mysterious than others. Numerous anecdotal collections tell of these happy accidents of discovery. Well known examples include Fleming's discovery of penicillin, Roentgen's discovery of X-rays, and Kekule's dreams that led to the discovery of the structure of benzene (Roberts, 1989).

A few works have dealt with the need to develop information system designs that take into account the tendency for scientific research to have a rationalist, unconscious or serendipitous basis. For example, in a paper titled "Information Retrieval Based on Patterns of Scientific Discovery," Harmon (1978) commented that information retrieval systems should be developed to accelerate and catalyze the discovery process. Likewise, Harter (1984) applied the traditional model of the cyclical process of scientific discovery to the task of online information retrieval. Nevertheless, most information retrieval design theories have continued to be based on simplistic query-response models which have dominated thinking since the beginnings of computer-based information retrieval research in the 1950s (Ellis, 1993, 1994; Pao, 1989).

Likewise, the nature and role of problem solving needs to be addressed in the study of scientific research and corresponding information use patterns. This need appears to be quite important in the complex area of medical and physiological research, wherein many Nobel Laureates are influenced by their education and indoctrination as clinical physicians. Cutler's medical textbook titled *Problem Solving in Clinical Medicine; From Data to Diagnosis* (1985) detailed the various problem-solving and diagnostic heuristics. In his pioneer work, *Knowledge Coupling; New Premises and New Tools for Medical Care and Education*, Weed (1991) proposed that problem-oriented medical record systems (POMRs) should be developed to couple clinical problem solving with all the knowledge that is known about the individual patient's problem for purposes of diagnosis and treatment.

In summary, the key works related to the nature of Nobel Laureate discovery patterns and knowledge use span diverse literatures. The above review encompasses several broad areas: the history of science; the nature of scientific progress; the prediction of discovery events; the sociology of Nobel Laureate science; the limited relevance of

many information need and use studies; the cognitive science movement, including the roles of the unconscious cognition and information encountering; the roles of rationalistic and empiricist perspectives; and the possible relevance of clinical problem solving and knowledge synthesis to the study of Noble Laureate research in physiology and medicine.

HYPOTHESES: DISCOVERY DYNAMICS AND CRITICAL RESEARCH INCIDENTS

The following hypotheses are based on a pilot study of twelve Nobel Laureate cases (presentation and acceptance speeches). The **first hypothesis** is that Nobel Laureate discovery patterns in medicine and physiology are characterized by the gradual acquisition of a critical but unorganized mass of knowledge which, upon being ordered and synthesized, produces the discovery outcome itself; the discovery outcome tends to consist of approximately seven basic components, reflecting the cognitive limits of human short-term memory. Because the process of knowledge accumulation requires from one to twelve decades, the incorporation of one or more key seminal concepts or themes provides initial direction and focus. Given a minimum set of elemental concepts, a potential discovery can be framed, additional concepts added, and finally, actualized as a discovery outcome.

The **second hypothesis** is that critical research incidents serve to start, stop, retard, accelerate, reorganize, redirect, or culminate research efforts. Examples of critical incidents include the researcher's discovery of data that contradict prevailing theories; serendipitous information encounters that involve experimental accidents, surprises, and impasses; intense narrowing of research focus; stopping to summarize results and author articles, or corroborations with colleagues. Critical events reveal patterns in the discovery process and indicate crucial knowledge synthesis events.

The **third hypothesis** is that Laureates who have completed medical education and clinical training tend to be habituated to the use of well-established clinical problem-

solving heuristics (rules of thumb). They use this modus operandi in their fundamental research. Examples of these heuristics according to Cutler (1985) include the use of clinical diagnostic routines that are based on clustering of signs and symptoms; syndrome recognition; data pattern building; proof by exclusion (differential diagnosis); and a concluding diagnosis or working hypothesis. Here too, clinical problem-solving heuristics can collectively reveal component parts of discovery patterns and knowledge synthesis incidents.

RESEARCH APPROACH AND CASE ANALYSIS

As explained earlier, the full texts of presentation and Nobel Laureate acceptance speeches are compiled in several volumes that have been published to cover the 151 Nobel Laureate awards in Physiology or Medicine from 1901 through 1990. The presentation speeches consist of introductory remarks by a leading scientist about the Laureates' work and are presented before the King and Queen of Sweden and a distinguished audience. The acceptance speeches are generally lengthy, ranging from approximately 10 to 50 pages of text, and consist of rigorous Nobel Laureate autobiographical cases or accounts. These accounts focus on predecessor contributions, theoretical explanation, the Laureate's own previous work, ideas of contemporary colleagues, explanations of the Laureate's chain of experiments, and the achievement of culminating insights that were crucial to the ultimate discovery. The accounts also serve as a rich source of quotations that reveal unusual insights regarding the nature of science or the particular object of investigation. Some Nobel Laureate remarks, for example, reveal the strong affective and aesthetic components of research enterprise:

> Some sciences are exciting because of their generality and some because of their predictive power. Immunology is particularly exciting, however, because it provokes unusual ideas, some of which are not easily come upon through other fields of study (Edelman, 1992, p. 31).

> There must be numerous homeostatic adjustments required of cells. The sensing devices and the signals that initiate these adjustments are beyond our present ability to fathom. A goal for the future would be to determine the extent of knowledge the cell has of itself, and how it utilizes this knowledge in a "thoughtful" manner when challenged (McClintock, 1993, p. 193).

> Early in my career I became convinced that current teaching concerning nutrition was inadequate, and while still a student in hospital in the earlier eighteen nineties I made up my mind that the part played by nutritional errors in the causation of disease was underrated. The current treatment of scurvy and rickets seemed to me to ignore the significance of the old recorded observations (Hopkins, 1965, p. 217).

This study analyses Nobel Laureate speeches drawn especially from 151 Laureate awards in Physiology or Medicine (Appendix A) compiled in the first six volumes (1901-1990). These accounts were selected according to the following main criteria: (1) cases to represent major subject areas as cardiology, endocrinology, genetics, immunology, microbiology, and neurology; (2) a representation of accounts from different volumes, to provide time sampling; (3) cases that provide relatively thorough and insightful explanations, or are elegantly revealing with regard to discovery dynamics and knowledge synthesis incidents. Other selection criteria, such as geographical origins or locations of Laureates, did not appear to be significant in the pilot phase of this investigation. The textual content of these selected cases is analyzed according to the content and critical incident analysis methodologies explained below. Additionally, because the present investigator is not a scientist, it was necessary to select the less esoteric, more understandable Nobel Laureate cases. Many of the speeches, particularly those in biochemistry and genetics, require subject expertise beyond that possessed by this investigator.

First, at a general level, this study employs content analysis, which serves as an unobtrusive social research method appropriate for studying scientific knowledge synthesis. Regarding content analysis, Babbie (1995, p. 311) writes: "Communications—

oral, written, or other—are coded or classified according to some conceptual framework." Krippendorff (1980, p. 21) gives the following definition: "Content analysis is a research technique for making replicable and valid inferences from data to their content." Another definition is given by Stone, et. al. (1966, p. 5) "…any research technique for making inferences by systematically and objectively identifying specified characters within text." Weber's definition gives an idea of the flexibility of this method:

> …a research methodology that utilizes a set of procedures to make valid inferences from text. These inferences are about the sender(s) of message, the message itself, or the audience of the message. The rules of this inferential process vary with the theoretical and substantive interests of the investigator.... (Weber, 1985, p. 1)

Content analysis has been widely applied to the topical, thematic and categorical analysis of written text in a broad range of subjects (Good & Scates, 1954). In library and information science, content analysis has been heavily used in indexing and abstracting and other areas of information retrieval and communication analysis (Baxendale, 1966; Fairthorne, 1969; Sharp, 1967; Taulbee, 1968).

Second, the study employs critical incident methodology. Flanagan (1954, p. 327), one of the psychologists who pioneered its use, defined it:

> By incident is meant any observable human activity that is sufficiently complete in itself to permit inferences and predictions to be made about the person performing the act. To be critical, an incident must occur in a situation where the purpose or intent of the act seems fairly clear to the observer and where its consequences are sufficiently definite to leave little doubt concerning its effects.

Andersson and Nilsson (1994, p. 398), who studied the reliability and validity of the technique and gave it a positive evaluation, gave the following definition:

> …a procedure used in the collection and analysis of incidents in which the holder of a position in a certain occupation has acted in a way, which, according to some criterion, has been of decisive significance for his success or failure in a task.

In the *Encyclopedia of Library and Information Science* (1971, p. 288), Shirey provided another definition:

> …a procedure for gathering factual information about behavior of individual members of a group involved in the performance of certain well-defined tasks or activities. The procedure is flexible ... it allows the researcher to apply a generalized set of principles which must be adapted to the specific situation under study….

Menzel (1966) reviewed critical-incident decision studies in the broader context of information need and use studies. Here, critical incidents are regarded as events stemming from decisions reached during the course of scientific or engineering work. An attempt is made to trace back from the decision to any information intakes that affected the decision. Consequently, to facilitate a study of critical incidents in a research and development environment at MIT, a "Solution Development Record" was devised (Allen, 1966). This investigation, then, applies critical incident analysis to the textual content of Nobel Laureate accounts to discern those events that were implicitly or explicitly crucial to research outcomes. These case accounts may likewise be viewed as solution development records.

A third somewhat minor but still relevant methodology involves the use of intellectual linkages, as expressed by citations between the Laureates and their scholarly colleagues. Laureates refer to or cite other scientists to acknowledge their contributions to the research effort as a whole or to specific critical research incidents. Likewise, Laureates assiduously tend to report their research findings to provide summaries for themselves and others and to establish or maintain intellectual linkages with the scientific community. In medical informatics, the nature of such intellectual linkages has been developed in major studies of the heuristics of clinical problem solving. In his classic work on clinical problem solving, Cutler (1985) explained how medical clinicians employ established heuristics to diagnose disorders or diseases. Because many Nobel

Laureates in this study were educated as physicians and possessed considerable clinical experience, their inculcated use of these clinical heuristics is examined to assess whether or not these heuristics carry over into their basic research.

Appendix B lists the major content analysis categories used in this study. These categories include critical incident and knowledge synthesis events and problem-solving heuristics.

The discovery and knowledge synthesis patterns of master researchers, as revealed by solution development records, can also reveal the nature of their associative reasoning. Floridi (1996, p. 46) discussed the need for new logical structures based on *ideometry*, "the study of significant patterns, resulting from a comparative and quantitative analysis of the domain of knowledge." He noted that relational and associative reasoning, along with visual thinking, were becoming as prevalent as linear, inferential, and symbolic processing. Nobel Laureates occasionally reveal their use of such advanced kinds of processing. This investigation points out several instances of Laureate associative reasoning and the underlying dynamics.

CONCLUSION

In summary, this effort involves the scrutiny of numerous Nobel Laureate autobiographical accounts of their own discoveries. The investigation employs textual content analysis, which is focused through the detection of critical incidents. These critical incidents include knowledge synthesis and research and problem solving events that influence research outcomes (Appendix B). The successful isolation of past discovery and information use patterns of these Laureates should serve to support future fundamental research. For applied research purposes, the isolation of such patterns can inform the design of future searching systems that support fundamental research in medicine and physiology.

The next chapter presents a pilot analysis of 20 Nobel Laureate speeches to discern some underlying themes and research patterns involved in the process of discovery. Chapter 3 extends the results of the pilot analysis through a more careful search for patterns related to a systems model of discovery. In turn, Chapter 4 serves to elaborate and formalize a General Systems Theory ontology (set of categorizations) that appears to be useful in explaining how past Laureate breakthroughs occurred. Chapter 5, the concluding chapter, reexamines the above hypotheses of the study, further discusses a systems model of discovery and its implications for search and research, and suggests some potentially productive, future research themes and directions.

Chapter 2: Basic Discovery Patterns: a Pilot Analysis

INTRODUCTION

This chapter outlines an initial, pilot analysis of 20 Nobel Laureate speeches that were presented in selected years between 1901 and 1984. The purpose of this chapter's analysis is to develop a rudimentary understanding of the Nobel Laureate research patterns through content and critical incident analysis, and to initially test this investigator's research hypotheses. The hypotheses propose that (1) Nobel discoveries are characterized by the acquisition and ordering of knowledge aggregates to produce a discovery; (2) critical incidents are key features in discovery processes; (3) the prior training of Nobel Laureate scientists, particularly in clinical problem-solving, condition their analytical frameworks; and (4) self-citation is a prominent practice among Laureates.

Where appropriate, quotations from the Laureates are included. In addition, cases are presented in chronological order to avoid selection bias and to gather a more representative sample from different time periods. The chapter begins with von Behring's 1901 account of his discovery of serum therapy and ends with Jerne's 1984 account of immune system dynamics.

EMIL ADOLPH VON BEHRING, 1901: "SERUM THERAPY IN THERAPEUTICS AND MEDICAL SCIENCE"

In 1901 Emil Adolph von Behring received the Nobel Prize for his pioneering work on serum therapy, especially its application against diphtheria. He reviewed the course of his research in his Nobel lecture, "Serum Therapy in Therapeutics and Medical Science"(von Behring, 1967). His investigations were founded on the prior works of Bretonmeau, Pasteur, Koch, Erlich, Loffler, Roux, Yersin, and others, as well as his own

career in experimental medicine. Von Behring went against the prevailing and entrenched dogma that infectious diseases were based on solidistic pathology, the idea that infection affected and spread through cells and tissue, rather than through humoral pathology. He noted, for example, that diphtheria was incubated in the tonsils (amygdala) and carried through the lymph vessels to fully affect a human. Likewise, he noted that animals, when experimentally inoculated in the blood or eye with diphtheria bacteria, would become quite ill. He thus proposed the use of antitoxin therapy:

> It is a humoral therapy, because its activity develops only within the fluid and solved components of the individual who is ill or threatened with illness. It has an anti-infectious action brought about by internal disinfection, but is, in this respect, in contrast to the anti-bacterial disinfectant treatment methods which...because its activity is only detoxication, we call it antitoxic. Because it does not influence the substrata of the diseased manifestations, the cells and organs, but only the *cause* of the disease, I call it aetiological therapy…. (von Behring, 1967, p. 11)

To reach this conclusion von Behring used the stable foundation of experimental medicine provided by his predecessors, conducted many trial-and-error experimental studies to formulate his hypotheses, and then carried out rigorously controlled experiments which confirmed his hypothesis. His development of antitoxic humoral, or serum, therapy led to diphtheria immunization and management in humans. Although he included only one formal citation, literature use patterns suggest that he gained fundamental knowledge and specific insights from about seven predecessors and colleagues over an 80-year time span; he then conducted a series of experiments and published a series of papers, which served to establish a "research trail" and to inform his subsequent experiments.

By way of observation, it can be noted that von Behring possessed considerable foundational knowledge at the outset by virtue of his education and experience. He acknowledges about 10 predecessors who helped establish the conceptual foundation for his work. This number accords with one hypothesis of this study that a limited number of

cognitive chunks are necessary to complete a manageable system of knowledge—in this case the etiology and pathogenesis of diphtheria. However, because of the relatively informal citations employed in the early 1900s, a sequential series of events that led to this discovery cannot be formally traced. Von Behring did, however, refer to his own sequence of findings that culminated in his discovery, and acknowledged the influence of his contemporaries.

CHARLES LOUIS ALPHONSE LAVERAN, 1907: "PROTOZOA AS CAUSES OF DISEASES"

Laveran (1967) received his Nobel Prize in 1907 "in recognition of his work on the role played by protozoa in causing disease" (*Nobel lectures, including presentation speeches and laureates' biographies: Physiology or medicine, 1901-1921*, 1967, p. 257). He engaged in systematic pattern building in medical protozoology to make his discovery of the microorganism responsible for the disease malaria. He systematically built on Pasteur's theory of germs and the discovery of vectors that caused "tuberculosis, glanders, pneumonia, typhoid fever, etc. during the years 1880-1890" (Sundberg, 1967, p. 259). This pattern building of knowledge was applied to the search for the cause of marsh fevers, such as malaria, during his tour as a military doctor in Algeria. Examination of blood samples from malaria patients revealed the presence of black particles called melanins and some entirely unknown parasitic bodies. Later investigations in the dangerous, marshy regions of Italy involved the analysis of 480 cases of malaria and led to publication of his first great work on the parasite *Traité des fièvres palustres* in 1884 (Sundberg, 1967, p.260). This great synthesis of knowledge provided the foundation for subsequent investigations of marsh fever. He noted the tremendous destruction caused by parasites in the blood involving the breakdown of red blood cells to produce melanin particles. This led him to look for parasites outside the patient's body that exist in the air, water or soil; however, his investigations produced negative findings. These negative

findings were still extremely important for they led him to conclude that marsh fever parasites underwent development in mosquitoes and thus became dangerous when inoculated into humans via mosquito bites. Here the role of analogy in knowledge transfer is illustrated. Laveran used work by Manson on the *Filaria* worm to demonstrate how the parasite was mosquito-borne. Laveran concluded that the new parasite was not a bacterium, but was some kind of protozoa despite the heavy influence of bacterial theory. From other marsh fever investigators, he tenaciously maintained his protozoa hypothesis through painstaking progress. He confirmed his hypothesis and by 1889 his work achieved recognition. Over the next 10 years an army of investigators around the world (including Ronald Ross, 1902 Nobel Laureate in Physiology or Medicine) confirmed the existence of malaria parasites in mosquitoes. Laveran's theory was then generalized to the realm of other diseases resembling malaria found in humans and animals. This led to an explosion of findings about protozoa as agents of a large number of diseases that occur in all parts of the world in nearly all warm blooded animals, especially in tropical or wetland zones. His experimental and theoretical work in Paris led to the original discovery of a great number of new *Trypanosomes* that are responsible for a broad range of parasitic diseases. "Laveran published his discoveries, sometimes in collaboration with other workers, in many articles and annotations, and later, in 1904 he gathered them together in one great work, so far unique of its kind: *Les trypanosomoes et trypanosomiasis*" (Sundberg, 1967, p. 263). His subsequent publications widened the discovery of the prevalence of parasitic diseases in Africa and elaborated on parasitic disease mechanisms. Laveran ends his presentation with an axiom attributed to Bacon: "Bene est scire, per causas scire," (1967, p. 271) which translates as "To know truly is to know through causes."

Laveran's discovery and information use patterns in this case demonstrate: (1.) careful pattern building based on blocks of knowledge from the literature and experimental findings; (2.) the importance of negative findings in the redirection of research; (3.) a tenacious persistence in developing and confirming hypotheses; (4.) the publication of a masterful state of the art compilations, and (5.) influence of his work on other scientists. Indeed, a scientist like Laveran can have a strong and durable catalytic impact on the work of other scientists, and can serve to redirect the focus of their investigations.

This discovery, above all, illustrates a grasp of a singular, fundamental concept that when generalized had a powerful multiplier effect in the production of medical knowledge. The discovery of the mechanism of one disease led to the discovery of several hundred associated disease mechanisms.

ALEXIS CARREL, 1912: "SUTURE OF BLOOD-VESSELS AND TRANSPLANTATION OF ORGANS"

Alexis Carrel (1967), 1912 Nobel Laureate in Physiology or Medicine, notes in his lecture that the ideas of replacing diseased organs with healthy ones, reattaching an amputated limb, or grafting a new limb on a patient after an amputation were not new. A major problem in transplantation was quickly reestablishing normal circulation through the transplanted structure. Carrel solved this problem. He received the Nobel Prize for his development of a new procedure for suturing lesions in blood vessels that ensured a free flow of blood at the suture site and prevented post-operative hemorrhage, thrombosis, and secondary stricture, and for his work in organ transplantation. In addition, he developed techniques for preserving sections of blood vessels for later transplantation.

As an experimental surgery researcher, Alexis Carrel's work was inherently mechanical and case-based. He drew minimally on the research of his predecessors and

contemporaries, citing mainly his contemporaries. His work was not what can be described as literature-dependent. Instead, he performed a series of transplantations, carefully recording his observations on surgical outcomes and complications. Here literature served very little as a platform for experimental research. What Carrel did do, however, was to publish his findings on each major experiment, thus providing a trail of literature on his research. The act of publication, then, served to fill this researcher's need to organize, clarify, and explicate his findings and reflections. He was not a literature user in the classic sense, but used the literature in the manner that one might put down a pathway of stepping stones across a stream.

Although he described a surgical procedure, it is interesting to note that he grouped the overall procedure into three basic approaches: (1) temporary haemostasis and preparation of the vessels; (2) suture (with termino-terminal anastomosis and termino-lateral anastomosis and latero-lateral anastomosis); (3) reestablishment of the circulation. These three approaches contain three basic sections and three subsections, or a total of six steps needed to suture blood vessels and transplant organs; six steps or techniques were therefore required. These six steps thus represent cognitive chunks in the overall required mental task. That is, all these steps make up an approach for successful vascular surgery in transplantation, grafting or reattaching an organ, tissue or limb. Carrel's suture technique was reasonably successful for its time, although other barriers, such as organ rejection and long-term success of transplants or attachments, continued as challenges in the area of surgery.

WILLEM EINTHOVEN, 1924: "THE STRING GALVANOMETER AND THE MEASUREMENT OF THE ACTION CURRENTS OF THE HEART"

In his "The String Galvanometer and the Measurement of the Action Currents of the Heart," Willem Einthoven (1965) described the research that resulted in his receiving

the 1924 Nobel Prize in Physiology or Medicine for his discovery of the mechanism of the electrocardiogram. He was also partly responsible for the design of the string galvanometer and he developed interpretations of electrocardiograms. Educated as a medical doctor and qualified as a general practitioner, Einthoven accepted a position as Professor of Physiology at the University of Leiden in 1885. At the University he was involved in research on human physiology.

He became interested in the *action current* of the heart in 1891. Publications by Burdon-Sanderson in 1879 and August Waller in 1887 and 1889 had focused attention on this phenomenon. Einthoven began his efforts to record the heart sounds with a Lippmann capillary electrometer. He developed a simple method of correction and in 1895 was able to derive an actual electrocardiogram from the curve produced by the capillary electrometer. However this process was laborious and tedious, so Einthoven began working on a way to directly record the heart's potential variations with time. In 1903 he solved this problem by modifying the Deprez-d'Arsonval "moving-coil galvanometer" to create the string galvanometer. The electrocardiograms derived from the capillary electrometer and the string galvanometer showed perfect agreement, thus proving that the actual time process of the potential variation of the beating heart had been recorded. He published his first detailed description of the instrument in 1909. For many years he continued his studies and developed interpretations of electrocardiograms that signified various cardiac diseases and conditions.

Through numerous experiments, Einthoven methodically developed the string galvanometer and thoroughly tested and analyzed the suitability of the instrument for a variety of purposes. To inform other doctors and scientists of his work and its ramifications he published articles and made lecture tours. His numerous publications illustrate his interest in research and clinical applications for this versatile device. His

research was clearly similar to that of an experimental biomedical engineer, with successive mechanical, electrical and anatomical experiments. Each experiment again informed subsequent experiments.

Always a practical man, Einthoven was also a visionary. In 1906, he even proposed that telecardiograms be made at a physiological laboratory from patients lying in a hospital at a distance. Today, telecommunications permit the routine use of electrocardiograms to monitor patients at a distance.

Again, this early Nobel Laureate episode is casually documented, making it difficult to trace rigorously the chain of events that led to his invention of the string galvanometer, which subsequently served as the basis for the electrocardiogram. Einthoven used six illustrations, Figures 1-6, to depict the basic mechanisms of the string galvanometer. His remaining illustrations, Figures 7-26, addressed diagnostic applications of his device. His illustration of the device, then, appears to reflect cognitive chunking into a manageable and understandable whole.

CHARLES NICOLLE, 1928: "INVESTIGATIONS ON TYPHUS"

The 1928 Nobel Prize in Physiology or Medicine was presented to Charles Nicolle for his series of investigations on the etiology, progression and treatment of typhus. Nicolle (1965) wrote that typhus usually flared up suddenly, causing serious epidemics. The incidence of typhus coincided with some other serious public calamities, such as war, famine or flood.

The essence of Nicolle's discovery was his observation that typhus patients ceased spreading the disease as soon as they were admitted to hospitals. They had their clothes removed, were bathed and then dressed in clean hospital clothes. Nicolle concluded that the infection was being spread by a parasite, the body louse, which appeared on the bodies of patients and in their clothing. Nicolle and his associates

conducted animal experiments at the Pasteur Institute in Tunis. They were able to demonstrate that lice served as vectors, spreading the disease by biting infected monkeys, and then by biting healthy animals or humans. Nicolle also discovered that the infection was not spread to new generations of parasites by the parent parasites. Therefore, as the infected adult lice died out, so did the epidemic. Nicolle also discovered that animals that contracted typhus developed resistance to the disease and recovered. Although these animals were infected and carried the disease, some animals would not manifest symptoms of typhus. This last discovery was a totally new concept at the time, and opened a new field of research in infectious diseases, which he termed "sub-pathology." As a consequence of Nicolle's work, typhus moved from being a terrible plague to being simply a contagious but avoidable disease.

This is an instance of one individual making an observation and acting on that observation. Although any number of physicians may have had the same observations, they either did not act, or failed to recognize the underlying theoretical significance. Nicolle's strong conviction drove his persistent efforts to test his hypotheses, and his drive that ultimately led to a breakthrough. But what was the source of such underlying theoretical significance? Nicolle appears to have been strongly conditioned by the systematic picture of infectious disease that was emergent at the Pasteur Institute. Nicolle emphasized sets of relationships between viral infections, environments conducive to the spread of infections, carriers, disease outbreaks, immunity, vaccination, and public health. Nicolle painted a specific systems picture when he noted that a louse can be infected by biting a human who had typhus. The typhus virus would then grow in the digestive tract of the louse, and its feces would become virulent. Humans contaminated with louse feces would then contaminate their hands by scratching the irritated skin, and

then typically infect their eyes (conjunctiva), an ideal entry point for an active virus. Thus, Nicolle resolved the mystery about the cyclical incidence and spread of typhus.

FREDERICK GOWLAND HOPKINS, 1929: "THE EARLIER HISTORY OF VITAMIN RESEARCH"

The 1929 Nobel Prize was awarded to F. Gowland Hopkins for his discovery of growth stimulating vitamins. Hopkins was also responsible for several other discoveries, including isolating and identifying the structure of tryptophan and glutathione, as well as establishing the Department of Biochemistry at Cambridge University. His account of his Nobel Prize winning discovery is given in his lecture "The Earlier History of Vitamin Research" (Hopkins, 1965).

In the early 1890s, Hopkins was a young, 28 year old, medical student working at Guy's Hospital, London. He became convinced that animal nutrition was being viewed too much from the perspective of energy requirements. During this period Hopkins decided that the part played by nutrition in the causation of disease was considerably underrated. He noticed the current treatments of scurvy and rickets seemed to ignore the significance of old recorded observations. He pointed out that in hindsight, before the end of the nineteenth century, there was ample proof that caloric intake, proteins, and salts were inadequate for the complete definition of nutritional needs. This led him into a more comprehensive investigation of nutritional needs.

From 1906-07 Hopkins conducted repeated dietary experiments by feeding lab rats diets with various fractionations of special food extracts. The purpose of these experiments was to isolate, identify, and quantify the unknown nutritional substances necessary for growth. Convinced he was right, he had to go against the rigid dogma in the field. Hopkins felt he had to have conclusive proof of the existence of the active substances prior to publishing his findings. Consequently, he continued working from

1907 until he was forced by ill health in 1910 to give up his research until the following year. In 1911 he reported his findings to the English Biochemical Club and his paper was finally published in 1912. For Hopkins, publication established his "ownership" of the research and served to disseminate this new knowledge to his contemporaries, who redirected their own research, verified his results and made additional advances in nutritional science. Hopkins notes that his 1912 publication exerted directive influence on the field, especially on American researchers at Harvard and in Baltimore. Consequently, this revolutionized the field and revised the accepted dogma, which had been the goal of the young medical student. No bibliographic citations accompany his lecture.

In recollecting his years of research, Hopkins stated he had no conscious knowledge of earlier experiments that pointed to the eventual results of his research. In fact, he noted that he wished he had known of similar work done about the same time by the Dutch researcher Pekelharing. The Dutch researcher's paper was not abstracted or mentioned in Maly's *Jahresbericht fur Thierchemie,* a title that Hopkins, and others in the field, depended upon to keep up with current literature. It was only after doing his own experiments and publishing his findings that he learned of work done by his predecessors and contemporaries. The earlier researchers failed, or otherwise could not follow up on their results, and thus were not in a position to draw the conclusions that Hopkins did a few years later. His work demonstrated, that ongoing research needs to be coupled with the research of contemporaries, as well as with that of predecessors, in order to obtain the "critical mass" of findings essential to a breakthrough. Additionally, Hopkins noted that significant scientific works could be overshadowed:

> So often in the development of science, a fundamental idea is foreshadowed in many quarters but has long to wait before it emerges as a basis of accepted knowledge. …the work and words of true pioneers lay forgotten because published when average minds were not ready to appraise them at their right value. (Hopkins, 1965, p. 212)

Hopkins noted that in 1929 the literature was so enormous and complex, and the picture regarding vitamins so uncertain, that the origin of the vitamin concept remained obscure. Hopkins thus points out key flaws in our system of recorded knowledge.

GEORGE R. MINOT, 1934: "THE DEVELOPMENT OF LIVER THERAPY IN PERNICIOUS ANEMIA"

Minot ended his lecture on the development of liver therapy for pernicious anemia with the following:

> I have pointed out to you, also, some of the studies that have been made as the result of demonstrating with Dr. Murphy that liver feeding is dramatically effective for pernicious anemia patients. It seems to me that one may expect in the future more information to be obtained which, directly or indirectly, will follow as the result of these observations. Thus, upon the foundations laid by previous investigators, do medical art and science build a structure which will in its turn be the foundation of future knowledge. (1965, p. 366)

In his lecture, Minot acknowledged his intellectual debts to specific researchers, recounting how as a young medical student he became interested in pernicious anemia. He also reviewed the background to and course of his and Murphy's research, and related how he and others continued their research in order to create an improved and more agreeable version of the therapy and to add to medical knowledge.

In 1912 while still a medical student, he became interested in pernicious anemia and began observing patients with that condition. Minot (1965, p. 357)wrote that it seemed to him "that something in food might be of advantage" to those patients. He observed that treatments in use at the time, arsenic, splenectomy, and blood transfusions, were of little help and the patients eventually died. In addition, he had noticed that certain signs and symptoms of pernicious anemia were similar to those of pellagra, sprue, and beriberi, all of which were caused by nutritional deficiencies.

> For centuries the concept that food bore a relationship to anemia had been vaguely expressed in the literature. It had been shown that liver and kidneys, rich in complete proteins, promoted the growth of animals, and that substances in liver

> could enhance cell division. It was likewise recognized that liver-feeding could benefit patients with sprue (Manson, 1883) and pellagra. (Minot, 1965, p. 358)

He called Co-laureate Whipple's 1922 paper on hemoglobin regeneration in dogs by liver and other foods "invaluable" and "fundamental and classical" (Minot, 1965, p. 358) and credited Whipple with establishing the quantitative basis for food's impact on anemia. Based on his personal observations and his knowledge of the work of others, Minot believed that a diet rich in liver would benefit patients with pernicious anemia.

To test this hypothesis he and Murphy began daily weighing a large amount of liver and feeding it to a group of patients. The results were gratifying. The success of the liver diet indicated that this anemia was probably due to a dietary deficiency and provided direction to researchers seeking the cause of pernicious anemia. This discovery also provided the impetus for research to determine what constituent in liver was responsible for the effect and to develop concentrated extracts for regular therapeutic use.

Minot clearly indicated that in his experience the increase of medical knowledge results from the physician's awareness of the work done by predecessors and contemporaries and reported in the literature; direct, personal observations of therapies and their effects; careful and exacting experimentation; and courage to deviate from the accepted dogma.

WILLIAM P. MURPHY, 1934: "PERNICIOUS ANEMIA"

Working with Co-laureate George Minot, Murphy developed and tested the liver diet therapy for pernicious anemia. Through additional research he developed a potent, economical and injectable liver extract. While the extract was primarily used to treat pernicious anemia, it also proved beneficial in treating blood cell disorders that accompany pneumonia, influenza and other diseases, as well as in some post-operative conditions.

In his brief lecture Murphy (1965) reviewed the work done by predecessor colleagues, starting with Thomas Addison who in 1849 had described the disease and suggested it be called "idiopathic" anemia. Murphy noted that similar cases were published by Barclay, Wilks, Bristowe, Lebert, Habershon, and others. He referred to a paper published in 1872 by Biermer, who suggested the disorder be called "progressive pernicious" anemia. Monographs on the disease had been published by Eichhorst in 1878 and, in 1883 by Laache of Christiannia. Murphy further noted that these publications presented a clinical picture of pernicious anemia, which remained unchanged through the 1920s and 1930s. He recalled that Fenwick, in his 1880 book, *Atrophy of the stomach*, indicated that it was generally accepted that an imperfection in the gastric juices gave rise to the deficiency in the blood produced.

Murphy's numerous references to the history of publication on pernicious anemia indicate an awareness of the publications and the intellectual linkages to his predecessors. Of his own work and publications he says, "…all of this has been described in our early papers, so that further details need not here be recited." (1965, p. 370) Murphy's clinically based experiments were first discussed in his 1926 paper in which he reported his careful observations of afflicted patients. He continued to observe this original group of patients through the next several years, thus revealing the persistence, diligence, and highly organized approach to research that characterizes most Laureates.

GEORGE H. WHIPPLE, 1934: "HEMOGLOBIN REGENERATION AS INFLUENCED BY DIET AND OTHER FACTORS"

Whipple began his Nobel lecture by saying, "Experiments usually have a past history or a genealogical sequence…." (1965, p. 346) indicating his awareness that science builds on the work of predecessors in a field and also that an individual scientist's work develops through a recurring cycle of hypothesis—experiment—evaluation of

results—revision of the hypothesis. He gives a chronological history of the development of the liver diet, his collaborators and occasionally their institutional affiliations, and topical experimental thrusts. In a footnote he stated that he did not attempt to review the field of hemoglobin regeneration and diet or the work of others. Instead his intent was to summarize his own work on the liver diet as a therapy for anemia due to blood loss in dogs. In the course of reviewing his experiments, he painted a picture of an exemplary researcher who devoted meticulous attention to detailed record keeping, and who conducted well thought-out, repetitive experiments. He carefully and incrementally constructed results, which were absolutely reliable.

Although educated in pathology and physiology as a medical doctor, Whipple worked chiefly in a lab with dogs as experimental animals. His efforts proved that nutrition therapy could be used successfully, over an extended time period, to treat anemia. A brief bibliography following his Nobel lecture consists of 23 citations. Of these, only two are citations to the work of others and one of those is to an article by Co-laureate George Minot. Here again Whipple's lecture and publications seem to function as an extended lab notebook. Whipple includes five tables and one figure (six items) to summarize his key groupings of data that cover relationships between nutrition and hemoglobin production in anemia. Here too, the processes of cognitive chunking and systematic hypothesis testing appear to be present.

HENRIK DAM, 1943: "THE DISCOVERY OF VITAMIN K, ITS BIOLOGICAL FUNCTIONS AND THERAPEUTICAL APPLICATION"

Henrik Dam (1964), Danish biochemist, in his lecture delivered in 1945 following World War II, portrayed his discovery of vitamin K, which is essential for the coagulation of blood and the prevention of hemorrhages in man and animals. Dam's discovery arose from his studies from 1928–1930 on the cholesterol metabolism of

chicks. In 1914, Gardner and Lander published the results of their experiments with chickens which had sterols removed from their diets. The results of those experiments indicated that chickens could not synthesize cholesterol and would not thrive on diets lacking sterols.

In 1928 Dam decided to repeat the Gardner-Lander experiments using artificial, practically sterol-free diets with vitamins A and D in the form of sterol-free concentrates added. Dam found that chicks did synthesize cholesterol and that the amount of cholesterol formed increased as the chicks grew and increased their body weights. In the course of these experiments, Dam unexpectedly observed that chicks on the diet longer than two or three weeks developed hemorrhages under the skin, in muscles, or in other organs, and their blood samples showed delayed coagulation. Interestingly, the hemorrhages also occurred in chicks given a daily supplement of cholesterol. The reasons for such hemorrhages remained enigmatic.

In 1931 a group of Canadian researchers published a description of this hemorrhagic disease in chickens. These researchers included Holst and Halbrook, who published their observation that the disease was caused by a lack of vitamin C. Apparently, they were not aware that Dam had observed this disease and had ruled out several possible causes of the hemorrhages including scurvy. Although Dam's work had been interrupted by the threat of a rising Nazi government, he again in 1934 began experiments using newly available pure vitamin C and proved that the disease was due to some previously unrecognized dietary factor. He continued his experiments to determine which plant materials or animal organs were the most potent sources of the unknown factor. In 1935 his research showed that the unknown substance was most plentiful in green leaves and hog liver, and he determined that it was fat-soluble. He characterized it as a new fat-soluble vitamin and gave it the designation vitamin K.

Vitamin K was discovered because Dam wanted to understand what caused the unexpected hemorrhages in the chicks in his cholesterol experiments. He began by repeating earlier experiments reported in the literature with improved ingredients and disproved the conclusion reached by his predecessors. Dam's summary did not include formal citations, but did occasionally mention the works of predecessor colleagues. Observing the hemorrhages and having no plausible explanation for their cause was a challenge that Dam felt compelled to take up. Through careful, systematic, repetitive experiments in his laboratory Dam was able to locate and finally identify the unknown factor, vitamin K.

Dam included 11 figures in his presentation, but Figures 5 and 6 and 8-11 were illustrations of variations of the same phenomena regarding vitamin K and prothrombin metabolic mechanisms. His presentation is rigorous and methodical, but still constrained to serve as a cognitively manageable holistic picture of his discovery. Dam also noted that his contribution was accompanied by similar but independent findings on vitamin K deficiencies by three different groups of colleagues during the late 1930s, when Dam was concluding his work. This observation points out the tendency of several scientists to converge on the same problem at about the same time, and to produce simultaneous discoveries.

ALEXANDER FLEMING, 1945: "PENICILLIN"

Alexander Fleming, 1945 Nobel Prize Laureate in Physiology or Medicine, reveals in his lecture (1964) his accidental discovery of penicillin. This important antibiotic, although very potent against some common human pathogens, generally was not toxic to animal cells, unlike earlier substances. Fleming's 1928 discovery was the result of a fortuitous, chance event. In the process of doing basic research he noticed that one of his cultures was contaminated by a mold growing on its surface. What was

significant was that the mold, later identified as *Penicillium notatum*, had apparently killed and dissolved nearby colonies of the *staphylococcus* bacteria. His research on penicillin determined not only what pathogens were susceptible to the antibiotic, but also, that if an insufficient amount of penicillin was administered the bacteria would become resistant to the antibiotic.

In his Nobel lecture, Fleming pointed out that earlier literature review and investigative work had no bearing on his discovery of penicillin.

> …I might have claimed that I had come to the conclusion as a result of serious thought…. That would have been untrue…. My only merit is that I did not neglect the observation and that I pursued the subject as a bacteriologist (Fleming, 1964, p. 83).

However, Fleming also pointed out in his 1929 publication on his discovery that the properties and potential use of penicillin in treating infections served as the starting point for other scientists, who went on to develop stable forms of pure penicillin for clinical use.

A bacteriologist, Fleming's work was the laboratory-based, fundamental research of an academic investigator rather than a clinician. For him, publishing his findings was an efficient way to disseminate the information to scientists, especially biochemists, who were better qualified to continue the process of creating a stable, pure form suitable for use in clinical trials and for eventual use by practicing physicians. Fleming included no formal citations in his summary speech.

It is interesting to note that Fleming used six figures in his presentation to illustrate various culture plates that revealed the impact of penicillin on different bacterial colonies, and the relative toxicity of phenol on leucocytes and its ineffectiveness against staphylococci. Fleming's use of six illustrations again appears to show the tendency for scientists to factor their overall tasks into workable subtasks or chunks in accordance

with constraints on human short-term memory. Each of Fleming's six illustrations seems to represent a sub-investigation, or part of a logical chain of proofs. Laboratory observations provided evidence to confirm or disconfirm various hypotheses generated through the course of Fleming's investigation. Apparently, scientific literature and the findings of predecessors played a key role in Fleming's overall education and development as a biologist, and the pre-hypothesis stages of his work, but a laboratory accident and subsequent laboratory trials, probably augmented by laboratory manuals, had a culminating impact in his post-hypothesis work. Each of his six illustrations reveal a key finding worthy of publication, but collectively the illustrations make up the whole of Fleming's discovery. Howard W. Florey (1964) and Ernst B. Chain (1964), Fleming's 1945 Co-laureates in the properties and structure of penicillin, used seven and five figures, respectively, to illustrate the key components of their discoveries. The use of seven and five figures appears to illustrate how human short-term memory limits serve to simplify scientific reporting for the convenience of both the reporter and the reader.

MAX THEILER, 1951: "THE DEVELOPMENT OF VACCINES AGAINST YELLOW FEVER"

Max Theiler's (1964) significant discovery involved the disease yellow fever, also known as "jungle fever." His work proved that mice could be infected with the disease, thus providing an inexpensive and reliable research tool necessary for the study of the disease in the laboratory. In the course of his work, he also discovered that inoculating the mice with serum from monkeys or humans infected with the disease caused the mice to become infected, thus successfully mapping the occurrence of the disease in men and monkeys.

During a course of long and arduous research he and his assistants transmitted the virus from one mouse to another repeatedly. This caused the virus to weaken until a

monkey could be inoculated with serum from the last mouse in the series and proved to be protected from infection by the virus. These results encouraged Theiler to develop a technique whereby a safe vaccine could be made that would protect humans from yellow fever. This involved developing a series of variant strains of the virus and conducting tests in mice, then monkeys, and finally humans. Although the idea of inoculation was not new, Dr. Theiler's work gave mankind hope of utilizing vaccines to conquer other diseases caused by viruses, thus significantly improving life for all.

Theiler's presentation appears to be relatively unremarkable, except for its conspicuous absence of formal reference to related literature. Instead, Theiler relied on a painstaking and extended series of experiments to produce a successful vaccine. His references to related research were casual and spotty.

H. GOBIND KHORANA, 1968: "NUCLEIC ACID SYNTHESIS IN THE STUDY OF THE GENETIC CODE"

Khorana received the Nobel Prize for his work systematically devising methods for synthesizing well-defined nucleic acids. This work was a prerequisite for the final solution of the genetic code. In his Nobel lecture, Khorana (1972) pointed out that the work of several predecessors established the idea that genes make proteins and that genes are nucleic acids. This fundamental concept provided the beginning of biochemical genetics. The structural chemistry of nucleic acids was developed step-by-step by researchers in many countries over 70 years. The year 1952 marked a climax in that work when Brown and Todd were able to elucidate the internucleotidic linkage in nucleic acids.

After the discovery and development of knowledge of the chemical structures of nucleic acids, two major tasks remained to be tackled: synthesis and sequential analysis. Khorana's laboratory concentrated on the chemical synthesis. It is noteworthy that he

cited the work of others in the 1950s and early 1960s which he credited with forming the foundation for his own successful work from 1963-1967, work that followed up on the observations and theories of other scientists and built on that foundation brick by brick, using experiments to verify theoretical predictions.

Khorana emphasized the interdependency of the work by researchers in science and especially those working to understand the genetic code. He stressed that his work was very much a group effort and underscored this in his lecture with numerous references to the work of his predecessors and contemporaries. Research in one lab using one technique served to verify and augment work done in another lab using a different technique.

His research involved hands-on work in the laboratory, building on the work of others and reporting his findings primarily through articles published in journals relevant to genetics and biochemistry. An analysis of his reference list indicates that he cites his own work only 38% (36 out of 94 references) of the time. Khorana included eight tables, seven figures, and six sections in his presentation, which again illustrates the use of production units or cognitive chunks to form a complete, systematic picture of his findings.

ALFRED D. HERSHEY, 1969: "IDIOSYNCRASIES OF DNA STRUCTURE"

The 1969 Nobel Prize was awarded to Alfred D. Hershey (1972) and two colleagues for their research on virus replication and genetics. In 1958 Hershey and his colleagues began to try to resolve a paradox in what was known about the genetic structures of bacteriophage particles. Physical evidence suggested that phages contained more than one DNA molecule and probably more than one type of DNA; however, genetic crosses revealed only one linkage group. Hershey began learning how to extract, purify, and characterize DNA molecules. As part of this work he and Joseph Mandell

developed a technique for the chromatography of DNA. He and Elizabeth Burgi then applied that technique in their research using DNA extracted from phage T2. Their research determined that the DNA was chromatographically homogeneous, and, that when subjected to a critical speed of stirring, the DNA formed a second chromatographic species in a single band that was not chromatographically homogeneous. At a higher critical speed of stirring, a third chromatographic species was formed. They postulated that the new species were half and quarter length fragments. These results showed that chromatographic behavior and shear depended on molecular length and that their starting material was uniform with respect to length. They verified their results by sedimentation analysis.

Hershey and Burgi lacked a method of measuring or weighing the DNA molecules. Fortunately, two other researchers, Irwin Rubenstein and C. A. Thomas, Jr., had come up with such a method but were having difficulty extracting DNA molecules. The two groups teamed up and used radiographic methods to measure the phosphorus content of the DNA molecules. Since the DNA and phage particle contained equal amounts of phosphorus, there could be only one DNA molecule per phage particle.

Hershey went on to study another phage species. He noted that this work led to three generalizations that are probably valid for all viruses: (1) Virus particles contain a single molecule of DNA. (2) These molecules are species specific, and are usually identical in virus particles of a single species. (3) Different viruses contain nucleic acids that differ in length and nucleotide sequence and in many unexpected ways as well.

Hershey noted that earlier researchers also studied the breakage of DNA by shear; however, it was through his work that the stepwise breakage at critical rates of shear was first noted and that observation was necessary to substantiate theory and complete evidence for molecular homogeneity. Hershey cited his own publications only 10 times

out of 27 citations (37%). He commented that his work on sedimentation of DNA in sucrose would have been considerably eased, if he had known of earlier work on sedimentation of enzymes by Martin and Ames. This obviously is an example of an information need that went unfulfilled.

EARL W. SUTHERLAND, 1971: "STUDIES ON THE MECHANISM OF HORMONE ACTION"

In his "Studies on the Mechanism of Hormone Action," Earl W. Sutherland (1992) summarized his discovery of adenosine 3',5'-monophosphate (cyclic AMP or cAMP), which serves as a second messenger inside the cells of organisms. He found that epinephrine, secreted from the adrenal gland, does not enter cell walls but instead activates AMP, which in turn, regulates internal cell environments. Sutherland's Nobel Laureate summary is notable for the following reasons: (1) he went against the prevailing research focus by studying hormone action at the molecular level rather than the cellular level; (2) he demonstrated a resourceful use of analogy and metaphor to generate hypotheses; (3) he relied heavily on the close support and stimulation of laboratory research teams; (4) he and his colleagues very painstakingly investigated long chains of successive hypotheses in order to build generalizations, thus employing an inductive "brick building" approach; and, (5) he finally developed a grand, schematic representation of the second messenger concept that served to explain his discovery of cAMP mechanisms and processes.

Sutherland and his colleagues depended predominantly on laboratory investigation. Ironically, their use of literature served the primary purpose of recording and explaining their findings. Of 78 references, only 37 (47%) included citations to authors other than Sutherland and his colleagues. Here it appears, surprisingly, that the explanatory and organizing process involved in authoring an article or monograph

supports the investigation and discovery more than does the process of drawing on the literature. Where Sutherland and colleagues did draw on the findings of others, they were attempting to serve the following purposes: (1) they used the literature to corroborate their own conclusions (their verified experimental hypotheses); (2) they had arrived at an impasse in their own research, and sought explanations elsewhere; (3) they were seeking information outside their area of laboratory investigation or expertise; and (4) they were attempting to generalize their findings to broader sets of physiological phenomena. Nevertheless, this case clearly demonstrates that the citation of one's own works supersedes citing the works of others, and that the authoring and reporting functions may serve to fulfill the information needs of researchers more than input from other researchers. That is, the authoring and reporting functions can provide an extension of laboratory journals and logs, periodic summarizations of positive and negative findings, invitations to colleagues for feedback, reports to financial supporters and superiors, and often, a prelude to continued or future research funding.

GERALD M. EDELMAN, 1972: "ANTIBODY STRUCTURE AND MOLECULAR IMMUNOLOGY"

Gerald Edelman, 1972 Nobel Laureate, in his "Antibody Structure and Molecular Immunology," noted that his work on the structure of antibodies was the first which attempted to "interpret the properties of the immune system in terms of molecular structures" (Edelman, 1992, p. 31). His research provided the impetus for further research in immuno-chemistry. Antibodies are the protein molecules that enable the immune system to recognize antigens, i.e., molecules foreign to the organism. The structural approach to antibodies gave rise to conceptual reformulations, which provided the molecular basis for selective theories of immunity first developed in the mid to late 1950s by Jerne and Burnet. A key idea from these theories, that molecular recognition of

antigens occurs by selection among clones of cells of different specificity already committed to producing the appropriate antibodies, became the central dogma of modern immunology. At the time many studies suggested that each cell made antibodies of only one kind and that in the daughter cells this specificity of antibodies was the same as that of the parent cell.

Antibodies are extremely large proteins and are very heterogeneous. These characteristics were major problems for researchers attempting the structural analysis of antibodies. Edelman assumed that the molecules, like many other proteins, were comprised of several chains held together by sulphide bonds. Consequently, he approached the first problem by reducing the disulfide bonds of immunoglobulin G and immunoglobulin M coupled with exposure to dissociating solvents like 6 M urea to produce polypeptide chains. Thus, Edelman was able to verify that immunoglobulin G was a multichain structure instead of a single chain as had been believed.

Having solved the problem of how to deal with very large molecules, Edelman still had to conquer the heterogeneity problem, which he characterized as the "main obstruction to direct analysis of antibody structure" (Edelman, 1992, p. 33). Two questions had to be answered. First, was the heterogeneity due to the conformation of the polypeptide chains, the most popular assumption, or was it a reflection of differences in the primary structure of the chains, an implicit requirement of the clonal selection theory? Second, if heterogeneity implied a large population of molecules with different primary structures, where could a sufficient quantity of homogeneous material be secured in order to carry out a detailed structural analysis?

Edelman capitalized on a discovery by Henry Bence Jones in 1847 to secure an adequate supply of homogeneous material for his analysis. Jones had described how some patients with multiple myeloma excreted urinary proteins that are antigenically

related to immunoglobulins. The Bence Jones proteins were readily obtainable in large quantities from urine, were homogeneous, and had low molecular weights. Edelman hypothesized that the Bence Jones proteins were synthesized by the myeloma tumor, but not incorporated into the myeloma protein, and therefore, were excreted into the urine. This hypothesis was confirmed by comparing the "light" chains of myeloma proteins with Bence Jones proteins. Further laboratory tests showed that in normal urine there were counterparts to the Bence Jones proteins that shared their properties but were heterogeneous. The experiments showed that the heterogeneity of antibodies was limited and that antibodies of different specificities were structurally different. The Bence Jones proteins were composed of different combinations of amino acids. From this it could be deduced that immunoglobulins must vary in their primary structure. This deduction, later confirmed, strongly supported the selective theories of antibody formation. Additional experiments comparing the "light" and "heavy" chains identified another source of antibody heterogeneity, the existence of immunoglobulin classes.

In closing, Edelman remarked that science is a communal enterprise and acknowledged the contributions of his friends and colleagues. He noted that the knowledge of antibody structure was developed through the work of many researchers and laboratories. While he cited the work of other researchers, citations to his own publications comprise 41.7% of the references in the bibliography. The majority of these self-citations occurred in the first part of his lecture where he recounted the work that earned him a Nobel Prize. In the later part of his lecture he mentioned the consequences of his work and the work that still needed to be done in molecular immunology.

RENATO DULBECCO, 1975: "FROM THE MOLECULAR BIOLOGY OF ONCOGENIC DNA VIRUSES TO CANCER"

The 1975 Laureates in Physiology or Medicine made a valuable contribution to the understanding of how a normal cell is transformed into a cancer cell. Genetic material in the cell is transformed by radiation, by exposure to certain chemicals, or by infection with tumor viruses. Renato Dulbecco (1992) and his Co-laureates worked with tumor viruses. Dulbecco's contribution was the key observation that the DNA of the virus entered the cell's nucleus and merged with the cell's DNA. This new genetic material was responsible for the unlimited cell growth—a property passed on to new cells as cell division occurred, and on to successive cell generations.

In the course of his medical education, Dulbecco found his true interest was in biology rather than applied medicine. Consequently, he went to work in the lab of the professor of anatomy, Giuseppe Levi, where he learned histology and basic cell culture. Also working in Levi's lab were Salvador Luria (a 1969 Laureate) and Rita Levi-Montalcini (a 1986 Laureate), the latter whom he credited as being a major influence in his life. He finished his MD degree in 1936 in morbid anatomy and pathology and served in the Italian army as a medical officer before and again during World War II and later in the Resistance. After the War, he returned to Levi's anatomy lab where he worked with his friend Rita Montalcini-Levi. She encouraged him to go to the United States where he could work in modern biology on the genetics of some very simple organism. Salvador Luria, who had been in the United States since the beginning of the War, returned briefly to Italy and offered Dulbecco a position in his own lab in the United States doing just that kind of research. After a couple of years Max Delbrück offered Dulbecco a position at Caltech. It was at Caltech that he began to work with animal viruses.

In the late 1950s Dulbecco's student and Co-laureate, Howard Temin, and a postdoctoral fellow, Harry Rubin, worked on the Rous Sarcoma Virus. It was their work that stirred Dulbecco's interest in the tumor virus field. Renato Dulbecco stressed the important roles of his peers in his scientific life, but also acknowledged the importance of students and other young associates, especially as research became more and more complex and required increasingly specialized skills.

> Perhaps more important than all this, the daily interaction through the years with a continuously changing group of young investigators shaped my work. …the actual path followed by my research was pragmatically determined by what could be done at any given time, and my young collaborators were an essential part of this process. I always did as much as possible of the experimental work with my own hands, but in the later part of my research career this became progressively less feasible, both because the demand on my time increased and because the increasing technical sophistication and complexities of the experiments demanded a great deal of specialized skills (Dulbecco, 1992, p. 231).

Literature seemed to be less important to Dulbecco than the knowledge, influence, and daily interaction with his scientist peers and a variety of young researchers with the specialized knowledge needed for the experiments. In his relatively brief bibliography, Dulbecco's own work accounted for only 29.1 % of the works cited, which illustrates that this highly socialized scientist tended to "pull" the findings and influences of colleagues into his own research. In contrast, other Laureates have tended to "push" their findings and influence outward to others largely through continual publications in which they cited their own works heavily. Likewise, Dulbecco demonstrated another aspect of his social connectedness—a great concern about the usefulness of science to society, particularly in cancer prevention.

Dulbecco's presentation consists of seven distinct sections: (1.) an introduction to the provirus, (2.) transformations of the virus, (3.) the viral transforming protein, (4.) cellular events in the transformation, (5.) the role of cellular mutations, (6.) prospects for cancer prevention, and (7.) biologists and society. This presentation is especially notable

because it presented a complete, systematic picture of this Laureate's discovery, grouped into seven components. In a sense, this seven-component system might be used as an example of a discovery or research template that can be used to characterize existing research, or even guide ongoing or future research.

BENGT SAMUELSSON, 1982: "FROM STUDIES OF BIOCHEMICAL MECHANISMS TO NOVEL BIOLOGICAL MEDIATORS: PROSTAGLANDIN ENDOPEROXIDES, THROMBOXANES AND LEUKOTRIENES"

The 1982 Nobel Prize in Physiology or Medicine was shared by three men for their discoveries concerning prostaglandins and related biologically active substances. Bengt Samuelsson was one of the co-recipients.

Samuelsson worked on the team, led by his teacher and co-recipient Sune Bergstrom, which determined the structure of the first prostaglandins. Next he spent a year (1961-62) at Harvard University studying theoretical and synthetic chemistry. Many prominent scientists, including Konrad Bloch and E. J. Corey, were on the faculty and provided a stimulating environment that Samuelsson said had a "profound effect" (1993, p. 117) on his future research. In 1964 research revealed a biogenetic relationship between polyunsaturated fatty acids and prostaglandins. The mechanism of the reactions involved was unknown. During this same time, Samuelsson established a laboratory and decided to study this problem.

His work focused on the transformation products of arachidonic acid and the biological effects of those metabolites, including endoperoxides, thromboxanes, and leukotrienes. Through laborious chemical, biochemical, and biological studies in several laboratories, Samuelsson and his co-workers isolated and determined the structure of several key elements in the prostaglandin system. His intensive research explained the interrelationships between the various components of this complicated biological system

and provided the potential to develop new therapeutic agents in clinical areas, especially in thrombosis, inflammation, and allergy.

Samuelsson used scientific literature to report his findings. The citations to the work of other scientists served primarily to show the impact of his work and its potential applications. As busy as he was in the lab, Samuelsson seemed to have been a fairly prolific author. Interestingly, a number of his citations to the work of others included publications that he edited. His editorial duties could have served to help him keep abreast of the newest developments in his field. These duties may also be an indication that he saw publishing as an important part of research. Oddly, he did not cite the last 15 references in his bibliography anywhere in his lecture. Of the 133 references, 54 (40.6%) are to works he authored or co-authored. Samuelsson includes six sections, nine figures and one table in his presentation. His organic chemical structure illustrations consist respectively of 6, 6, 6, 9, 6, 7, 10, and 14 chemical reactions or transformations, an average of 8 reactions through the set.

BARBARA MCCLINTOCK, 1983: "THE SIGNIFICANCE OF RESPONSES OF THE GENOME TO CHALLENGE"

Barbara McClintock (1993) was honored with the 1983 Nobel Prize in Physiology or Medicine for her discovery of mobile genetic elements, which she named control elements because they altered the function of nearby genes. Working completely alone using simple tools and systematically repeating experiments, she uncovered how genes are organized on chromosomes and how genes may change place and thus alter their function. Although she used maize in her research, McClintock realized that mobile genetic elements would probably be found in the genomes of insects and higher animals. Her work garnered little attention because her discovery was overshadowed by the discovery of genetic information in the structure of DNA. Geneticists had trouble

accepting her findings because her discovery ran contrary to the accepted paradigm and, also, the state of the art in molecular genetics at the time made it impossible to verify the existence of control elements.

Eventually the development of new tools made it possible to verify her monumental discovery. From the mid-1960s through the 1970s the significance of her discovery to medicine was recognized many times. Counterparts of the mobile genetic elements that she found in maize have been found in bacteria, animals, and humans. These elements play a part in bacteria becoming resistant to antibiotics. The transposition of genes, provide building blocks that enable animals to develop antibodies to an almost infinite number of foreign substances. Cancer researchers have discovered that in some forms of cancer the growth regulating genes (oncogenes) have moved from one chromosome to another.

McClintock began examining the behavior of broken ends of chromosomes in 1931. The knowledge and experience she gained in experiments over the next thirteen years prepared her to conceive the 1944 experiment that gave rise to her discovery. It was only after many repeated observations that McClintock's analysis led her to conclude that she was seeing a basic phenomenon, and that she had to determine what it was that one cell had gained, and the other lost. From 1948 through 1951, she carried out very advanced experiments and mapped several families of control elements for maize. She persevered in her research developing experiments and conducting repeated tests even though many geneticists would not accept her findings. Her experimental observations led her to questions that needed answers. To find the answers she developed hypotheses that she then tested experimentally. She reported her findings to her colleagues through journal articles, conference papers, and private correspondence. An examination of the literature, revealed that her work was vindicated by later researchers, who verified her

discovery, extended it, and explored its ramifications. In her reference list, 40% of the citations are to her publications. The references cover the period 1918 through 1983. Twelve of the author's 14 publications were published prior to 1952; and, 1951 is the halfway point in this time span. Her presentation consisted of seven parts: (1) an introduction, (2) an experiment, (3) effect of x-rays on chromosomes, (4) description of a telophase nucleus mechanism, (5) entry of a ruptured chromosome end into a telophase nucleus, (6) further examples of genomes to stress, and (7) conclusion.

NIELS K. JERNE, 1984: "THE GENERATIVE GRAMMAR OF THE IMMUNE SYSTEM"

In his presentation speech, Hans Wigzell calls Jerne "the great theoretician in modern immunity" (1993 p. 203) whose "visionary theories enabled modern immunology to make major leaps of progress." (1993p. 204) What is most remarkable is that Jerne's Nobel lecture illustrates the importance of analogy and metaphor in the inter-disciplinary cross-fertilization of ideas. Jerne paired the seemingly irrelevant fields of linguistics (generative grammar) and the dynamics of antibody structures and mechanisms.

Although the similarity between language and the immune system is not obvious, a scientist of Jerne's stature was able to see it, and he noted that immunologists sometimes borrowed words from linguistics. To him, the immune system's remarkable ability to assemble molecules into specific antibodies for substances unknown previously is like the ability of language to assemble new, intelligible sentences by using grammar. He likened the repertoire of the immune system to a lexicon of sentences able to respond to any antigen sentence encountered. He quoted the linguist Noam Chomsky to explain the appropriateness of this analogy and the use of linguistic terminology.

> The central fact to which any significant linguistic theory must address itself is this: a mature speaker can produce a new sentence of his language on the appropriate occasion, and other speakers can understand it immediately, though it is equally new to them…. Grammar is a device that specifies the infinite set of

> well-formed sentences and assigns to each of these one or more structured definitions. Perhaps we should call such a device a generative grammar…which should, ideally, contain a central syntactic component…a phonological component and a semantic component (Jerne, 1993, p. 220).

Chomsky's term for the set of all possible sentences in a language is "open-endedness" which to Jerne also was appropriate for describing the "completeness" of the antibody "repertoire."

Jerne also drew on Leonardo da Vinci's use of mirror writing to explain how antibodies mirror antigens. The antibody "sentences" contain partial mirror images of the antigen "sentences" they are supposed to recognize and combat. These partial mirror images are already present in the immune system before the introduction of the antigen. This "deep" structure, another Chomsky term, of the immune system and its innate generative capability resides in the DNA segments of certain chromosomes. Chomsky, pioneer of the generative approach to grammar, argued that young children learn language easily because of certain innate, deep structures, universal characteristics that must somehow be coded in DNA.

Another remarkable feature of Jerne's work was his great dependence on three-dimensional visualization of antibody systems and their dynamics (molecules, cells, and complete antibodies). In his lecture, Jerne was painstakingly methodical in sketching antibody mechanism in two-dimensions, the natural limit of flat displays, but then verbalized three-dimensional phenomena. Clearly, he could have used today's information technology that simulates and graphically illustrates three-dimensional phenomena. Hence, contemporary work in the emergent field of information visualization (Tufte, 1990) appears to be essential to the basic research enterprise, here and elsewhere. Watson, in his notable work The Double Helix (1968) drove home the point that Watson and Crick's realization of the double helix form served to suddenly coalesce nearly all

their findings about DNA molecules. Multidimensional simulation and visualization capability appear to be requisite to the progress of research in many areas of medical and physiological research (Zhu & Chen, 2004).

Jerne was a mature scientist when he began making significant contributions to the study of the immune system. Even with his years of experience as a biologist, he was surprised to find that the complexity of the immune system exhibited similarities to human language, and that this type of cognitive body system evolved without any apparent assistance from the brain.

His presentation is not sectioned into parts, but instead includes 11 figures to illustrate the key components and mechanisms of the immune system with corresponding linguistic homologs. His references are sectioned into 11 books and 37 articles. It is noteworthy that in his interdisciplinary synthesis he cites only two of his own works among 48 works cited. In this interdisciplinary work, literature usage appears to have played a large role. Perhaps, then, the use of literature assumes more importance in interdisciplinary research that it does in single-discipline or laboratory research.

CONCLUSION

This lengthy chapter has analyzed Nobel Laureate addresses, each of which summarized respective research journeys that culminated in a significant discovery. What lessons can be learned from this pilot analysis? First, all Laureates tended to be highly systematic, rigorous, methodical, persistent, relentless, and even stubborn in their pursuit of scientific truths. They were not afraid to go against prevailing paradigms, viewpoints or dogmas. They proved to be excellent laboratory investigators and/or field observers. They learned from negative findings. They were indeed exemplary scientists and even artists during the conduct of research. Second, the Laureates all employed systematic, holistic portraits of their findings, and their reports and/or illustrations seemed to consist

of syntheses of roughly seven cognitive components or chunks. For example, von Behring, Laveran, Niccole and Theiler all presented similar and systematic pictures of the transmission and spread of communicable diseases, hosts, vector, immunization, resistance, and so on. Third, critical incidents did not seem to play a large role in their research, except in the case of Fleming's discovery of penicillin. Minor critical incidents were noted in some Laureate accounts, such as chance encounters, but such incidents tended to play a relatively minor role. Fourth, Laureates who were educated as physicians tended to gravitate strongly toward laboratory or field science. While clinical training is apparent or even important in many accounts, the use of scientific methodology, hypothesis framing, experimental design, evaluation, hypothesis revision, is universally apparent and critically important. Fifth, Laureate publication practices revealed that about one third of their citations are to their own previous work. For Laureates, publication appears to provide extended laboratory notebooks that primarily serve to compile and summarize their findings and to report successive replications of experiments. Publication also provides a means of reporting to colleagues, showing accountability to superiors, or justifying past or future funding. The actual use of literature to inform research plays an important role, but that role pales in comparison to the critical role of laboratory or field investigation to secure strong primary data. Close working associations with colleagues also tended to be far more important to the Laureates than their reliance on scientific literature.

The key insight gained from this analysis is that among the Laureates' accounts analyzed, all scientists strongly tend to employ a systems paradigm. In fact, the discoveries per se might be said to consist of systematic conceptual representations of normal or pathological anatomical and physiological processes, whether they be at the cellular, organ, or organism level of analysis, or some combination thereof.

This pilot study reveals that the first hypothesis proposed in Chapter 1 appears to be correct, that is, Laureate discovery patterns are characterized by the gradual acquisition of a critical but unorganized mass of knowledge that, upon being ordered and synthesized, produced the discovery outcome itself. What this pilot analysis revealed was that the Laureates reviewed tended strongly to employ some sort of systems schema to consolidate and organize findings, and they appeared to do this consistently throughout all the cases. This systems insight is the strongest finding of this pilot analysis, from this investigator's viewpoint. Accordingly, the subsequent chapters are devoted to a reexamination of the pilot cases reviewed in this chapter from a systems perspective. Chapter 4 introduces additional cases.

The second hypothesis states that critical research incidents serve to start, stop, retard, accelerate, reorganize, redirect, or culminate research efforts. This investigator found to her surprise that the pilot cases revealed very little tendency of the Laureates to be driven by critical incidents during the course of their research. While it might be interesting to entertain the stereotypical view that these scientists are nearly always inspired by sudden flashes of creative insight, this stereotypical view did not appear to be applicable in nearly all of the pilot cases reviewed. Only in the case of Alexander Fleming's 1928 accidental discovery of penicillin, was there a serendipitous critical incident, and this was incidental to his research project at the time. Undoubtedly, other Laureates were influenced by critical incidents, but these were not important enough to be emphasized in their discovery accounts. By and large, the pilot cases reveal that the Laureates are painstakingly methodical, extremely diligent, and highly persistent in their research pursuits. Perhaps, the old aphorism that success stems from 99% perspiration and 1% inspiration holds true in attempts to characterize Nobel Laureate research success. Above all, Laureates are doggedly persistent in their research. Therefore, the

second hypothesis, that critical incidents play a key role in Laureate research, is only minimally supported. The analysis in this chapter is of a largely qualitative nature, but the critical incident hypothesis simply did not appear to be supported sufficiently to direct the remainder of this investigation.

The third hypothesis is that Laureates who have completed medical education tend to be habituated to the use of clinical problem-solving heuristics and that they deploy clinical problem solving as a modus operandi in their research. This hypothesis is partially confirmed, particularly in cases involving the investigation of communicable diseases, such as von Behring and Laveran; nutritional research, as in Hopkins, Minot, Murphy and Whipple; suture of blood vessels in Carrel; and the string galvanometer in Einthoven. Clinical problem solving, particularly pattern building, came into play especially in these earlier cases, but laboratory experimentation assumed a larger role. In the more recent pilot cases, laboratory research and experimentation assumed the key role in Laureate investigations. For the most part, Laureates were driven by the propensity to experiment over and over until they achieved replicable results. Their publications, in fact, often appear to be successive extensions of their laboratory notebooks. Therefore, the third hypothesis, while interesting, did not impress this investigator as being of sufficient importance to pursue in light of the strong first hypothesis involving the use of systems concepts. Medically-trained Nobel Laureates were clearly scientists first and clinicians second.

Given the emergence of the potentially overriding significance of the first hypothesis and the need to delimit this dissertation investigation, the following chapters concentrate on an exploration of systems models of research. Chapter 3 further analyzes the cases presented in this pilot chapter to explore the concept that systems models are

the key drivers of Laureate research and discovery. Chapter 4 presents a systems categorization/ontology of Nobel Laureate discovery patterns.

Chapter 3: Exploratory Analysis: Emergence of a Systems Model of Discovery

INTRODUCTION

This chapter reexamines the collective set of pilot discovery cases summarized in the previous chapter, and presents a systematic pattern of discovery that appears to be common to the previous chapter's set of discoveries. The emergence of the systems idea came to this study's investigator gradually, resulting in the need to evoke the entire body of knowledge known as General Systems Theory. Accordingly, this chapter summarizes the General Systems model, introduces new systems terminology, and proposes the deployment of a General Systems template for the analysis of Nobel Laureate discovery cases presented in the next chapter.

ANALYSIS OF PILOT CASES

This section analyzes the set of cases presented in the previous chapter and records general observations about each discovery case. The first previously presented discovery was that of von Behring, 1901, who reported on his work in serum therapy and the use of serum as an inoculation against diphtheria. By way of general observations, it is noteworthy that von Behring had built his own thorough foundation of knowledge in the basic biomedical sciences, as well as in clinical and experimental medicine. His extensive knowledge enabled him to discern disease patterns from a broad, holistic, rather than from a reductionistic viewpoint, to summarize and chunk information from his scientific predecessors, and to complete a manageable system of knowledge regarding the etiology of diphtheria and its pathogenesis via the lymphatic system. He further used systematic experiments to reduce uncertainty and successfully used inoculation against diphtheria, which served as an anti-toxin and for detoxification purposes. Von Behring

went against entrenched dogmas of the time, which claimed that infections spread through cells and tissues rather than through humoral pathology. Nevertheless, von Behring maintained a high degree of scientific skepticism, was holistic, systematic, and rigorous in his experimental sequencing and analysis, and deployed sound hypothetical-deductive logic throughout his discovery episode.

Laveran, 1907, investigated "Protozoa as Causes of Diseases" with a focus on marsh fevers such as malaria. He systematically built on Pasteur's theory of germs and the discovery of various communicable disease vectors, which led him into a search for the cause of marsh fevers throughout Algeria and Italy. He compiled his findings and insights in an 1884 book, in which he noted the occurrence of tremendous parasitic destructions of red blood cells. In turn, these insights prompted a further search for marsh fever parasites carried by mosquito vectors. He confirmed his protozoa hypothesis, which led to expanded research on the existence of malaria parasites, especially in tropical or wetland regions. His discoveries were increasingly generalized to *Trypanosomes*, which in turn were responsible for an ever-broader range of parasitic diseases. Thus, Laveran engaged in a systematic pattern of block building of knowledge, deployed rigorous experimental routines and logic, published systematic treatises, and thereby made breakthroughs in etiology and epidemiology. Probably the most powerful insight gleaned from the present analysis is that Laveran discovered a singular fundamental concept that had a powerful multiplier effect in the production of systematic medical knowledge: the mechanism of one disease was eventually associated with mechanisms of several hundred other diseases. It can be noted that the term "general" in General Systems Theory appears to be highly applicable throughout the present investigator's analysis of Laveran's discovery.

Carrel, 1912, reported on the "Suture of Blood Vessels and the Transplantation of Organs." He was apparently not an ardent user of literature, but showed a strong preference for experimental, case-based surgery. However, he did publish what amounted to a systematic trail of research findings in which he formulated surgical procedures for the preparation of vessels for transplantation, suture and reestablishment of circulation. Six mental tasks or cognitive components served as a working approach to vascular surgery in transplantation, grafting, or reattachment. In summary, Carrel developed a successful system of vascular surgery to support the replacement or modification of organs, tissues, and limbs -- all based on identifiable system or subsystem components.

Einthoven, 1924, devised the string galvanometer to measure dynamics of heart currents, which led to the discovery of the mechanism of the electrocardiogram. Einthoven's work, it can be observed, produced both a conceptual system regarding the anatomy and physiology of the heart, and what eventually would be an electro-mechanical system that provided the basis for the electrocardiogram. He used six illustrations to represent the basic mechanisms of the string galvanometer, and 19 illustrations to explain, through the interpretation of a long series of experiments, how the electrocardiogram could be applied to the diagnosis of a large number of heart conditions. His illustrations clearly depict systematic patterns of cognitive chunking into understandable wholes.

Nicolle, 1928, reported on his systematic investigation of the cycle related to the etiology, pathogenesis, spread and containment of the typhus virus. Nicolle identified the louse as the sole vector in the spread of typhus. In systems terminology, the louse (a cytoskeleton with motor function) would bite (ingestor function) a typhus-infected organism (monkey or human), and ingest or in-take infected bodily fluids. The typhus virus would then reproduce and multiply in the louses' digestive tract, and eventually be

extruded in the louses' feces onto the skin or boundary of a human or other organism. Humans would, for example, scratch their irritated skin and touch their eyes—an ideal entry point—or otherwise ingest the infected louse feces. Hence, the growth cycle transmission cycle of the typhus virus would be complete. Nicolle provided an excellent example of rigorous, systematic thinking.

In 1929 Hopkins reported on his findings in early vitamin research. In the 1890s, Hopkins had observed that the prevailing explanation of complete nutrition, then based on calories, proteins, and salts, appeared to contain notable gaps. His investigations into scurvy and rickets illustrated that these diseases did indeed have a nutritional basis despite the fact that animals and humans suffering from them did not appear to be deficient in calories, protein, or salt. He ignored the rigid, prevailing nutritional dogmas of the time and conducted repeated dietary experiments on laboratory rats. Hopkins waded through voluminous amounts of complex and confusing bodies of biochemistry and nutrition of literature, all of which appeared to be in disarray at the time. He noted that the work of true pioneers had been lost and drowned out in the morass of literature. His systematic treatise on vitamin research established his "ownership" of his discovery of growth vitamin stimulants, and his other discoveries on tryptophan and gluathione. His findings served to both recast the prevailing paradigm of nutritional medicine and to redirect and make advances in nutritional science worldwide. Therefore, Hopkins converted an incomplete and fallacious systems paradigm into one that was a complete and ordered set of systematic findings.

Minot's 1934 report, "The Development of Liver Therapy in Pernicious Anemia," was the result of inquiries that began in 1912 while he was still a medical student. He noted that prevailing treatments for anemia, that is, arsenic, splenectomy, and blood transfusions, were of little or no help, and that pernicious anemia was similar to several

nutritional deficiency diseases. Minot utilized the results of Co-laureate Whipple's work on hemoglobin regeneration and experimented with Co-laureate Murphy on the nutritional benefits of a liver diet to treat pernicious anemia. Co-Laureate Murphy went on to develop an injectable liver extract that was even more potent in treating pernicious anemia. Murphy had systematically synthesized much of the previous century's research, which enabled him to complete his picture of pernicious anemia and develop liver extract as a dietary input. In a similar fashion, Co-laureate George Whipple had built a sound foundational synthesis of his predecessors' work, which enabled him to conduct a long series of experiments, successively refine his hypotheses and experiments, and meticulously document these experiments. It can be noted that all three co-Laureates zeroed-in on the nutritional input side of metabolism, which resulted in remissions of pernicious anemia. All three Laureates had painstakingly synthesized a systematic picture of the metabolic disease mechanism and its pathology and cure. Thus, at the cellular and biochemical levels, the erythrocyte and hemoglobin levels, a true systems picture emerged.

Henrik Dam, 1943 Laureate, reported on his discovery of vitamin K as an essential dietary component for the prevention and cure of hemorrhages. Here again, his analytical focus was on the input side of physiological systems—those associated with the development of hemorrhages in chicks. Through a series of trial and error experiments, both Dam and his colleagues experimented by withholding sterols from chick diets to confirm the belief that cholesterol production was associated with healthy growth; indeed it was, up to a point. Dam was surprised to see the development of hemorrhages in chicks given vitamins A and D and their production of adequate cholesterol. While his colleagues experimented unsuccessfully with vitamin C, Dam looked for gaps in nutritional knowledge and experimented with the administration of

nutrients from green leaves and hog liver. This series of experiments led directly to his discovery of vitamin K and the realization that this vitamin was essential in the blood clotting process. Here, Dam's explanation filled a gap in systematic metabolic knowledge by plugging in a missing, hitherto unknown vitamin component. Incidentally, Dam used five basic figures and illustrations in his presentation (out of a total of 11, but six figures or illustrations were elaborations of those among his five basic illustrations). These five representations serve to illustrate how knowledge is chunked into systematic, cognitively manageable wholes. This chunking phenomenon is apparent in many or most of the Nobel Laureate presentations, and is discussed later.

Alexander Fleming's accidental discovery of penicillin is well known. In 1945 he reported on how one of his bacterial cultures had been contaminated by a mold growing on its surface that killed nearby colonies of *staphylococcus* bacteria. This mold was later identified as *Penicillum notatum*. Of particular interest in his presentation is his use of six illustrations of culture plates that demonstrated the impact of *Penicillum* as a bactericide. Each of these six illustrations depicts separate sub-investigations, or parts of a logical chain of deductions that served to make up the whole of Fleming's discovery. Likewise, Co-laureate Florey used seven illustrations and Co-laureate Chain used five illustrations to represent their work on the properties and structure of penicillin. In systems terms, it might be observed that organisms (the bacteria) were affected by a lethal input (mold) that killed them. Here we can clearly observe how these scientists developed and depicted a systematic and cognitively manageable scientific model, as well as the corresponding operation of an object system (actual bacterial input and processing).

In 1951 Max Theiler reported on his development of vaccines against yellow fever. Theiler experimentally spread yellow fever by injecting mice with serum from monkeys or humans who had yellow fever, thus demonstrating the spread of the disease.

In turn, he successively injected other mice with increasingly weaker, contaminated serum, until the serum could be used to inoculate the last mouse in the series. That is, different strengths of viral potency in serum inputs resulted in either disease, at high dosage levels, or immunity, at low dosage levels. Inputs affected each organism's systems at the cellular, tissue and organ levels with differing results, depending on dosage. Here, the cause and effect relationships are made apparent at different systems levels.

Khorana's work on the genetic code and nucleic acid synthesis, reported in 1968, is somewhat noteworthy because he used eight tables, seven figures and six sections in his presentation. These features of his presentation again can be seen as elements, or chunks, of his cognitively manageable, systematic representation of nucleic acids, genes or proteins. In turn, the actual object systems of genes or proteins are represented in terms of their synthesis (the formation of a complete system at the molecular level) and their systematic conceptual definition.

In 1969 Alfred Hershey and colleagues reported on successfully observing and measuring the key characteristics of bacteriophage particles and DNA molecules, largely through their refinement of DNA chromatography. Thereby, they were able to represent the essential characteristics of various virus species as entire systems. Their representations used a single species-specific molecule of DNA. The DNA molecule for each species varied according to the length and nucleotide sequence. Thus, the Laureates were successful in representing the key components of viral systems and their DNA subsystems fully and accurately. In their research, it can be noted, the object system's characteristics had been hitherto unknown or inaccurately conceptualized, but the researchers shed light on the workings of an entire class of microorganisms through a basic DNA systems representation.

Sutherland is notable for his work on the mechanism of hormone action (cyclic AMP or cAMP), reported in 1971. He went against the prevailing research thrust by studying hormone action at the molecular systems level rather than the cellular level. This finer focus enabled him to develop a grand, schematic representation that explained the importance of cAMP mechanisms and processes. He noted that the compound epinephrine did not enter cell walls but instead activated AMP, which regulated internal cell environments. It is remarkable that he went from the higher cellular systems level to its molecular subsystem levels to finally come upon the mechanism of hormone action. His analysis thus dealt with and revealed the more precise dimensions of cellular system functioning. Additionally, this case very clearly demonstrated the imperatives of both representing and dealing with the entirety of object systems and their subsystems, which appears to have been far more important than building on the works of predecessor scientists. The systematic summarization of laboratory findings can at times be more important than building on the record of previous knowledge. This systematic summarization, however, probably supported initial or continued research funding, whereas even extensive literature citation might not always serve to attract research funding. Empiricism in systematic science can override reliance on the supposedly cumulative scientific record.

Gerald Edelman received the 1972 Nobel Laureate for his discovery of the complexity of antibody structures and the dynamics of molecular immunology. Earlier, it was believed that immunoglobulin G possessed a single chain structure, but Edelman discovered that it was a multi-chain structure, and that other very complex arrays of heterogeneous antibody structures exist, including “heavy” and “light” chains of antibodies. Here, it can be observed that Edelman progressed from very rudimentary notions of antibody structures and immunology to successively refined, precise notions or

representations. While single chain theories were far too simple, Edelman provided multi-chain theories that could explain the precise immunological dynamics that had troubled investigators. It is probably fair, then, to classify Edelman as a molecular systems refinement pioneer.

Renato Dulbecco and his colleagues reported on the molecular biology of certain DNA viruses and their etiological relationship to cancer in 1975. He had noted that radiation, chemicals, and tumor viruses, specifically the provirus, penetrate cells and cause mutations in their DNA, resulting in altered, new generations of cells with unlimited cellular growth. It is quite noteworthy that Dulbecco and his colleagues depicted provirus-induced carcinogensis through the use of seven sections in his written account: (1) introduction, (2) transformations of virus, (3) the activating protein, (4) cellular transformation events, (5) cellular mutations, (6) prospects for cancer prevention, and (7) social implications. The researchers presented a complete systematic picture of their discovery. To this day, their account exemplifies the discovery process. Their portrayal of the discovery process can potentially serve to build a discovery or research template to explain existing research patterns or guide ongoing or future research endeavors. This case indeed provides key clues for those involved in studying the dynamics of discovery.

In 1982 Bengt Samuelsson shared the Nobel Prize with two colleagues for their discoveries concerning prostaglandins and the associated biochemical dynamics. Samuelsson transformed relatively simplistic conceptions of prostaglandin systems into more rigorous and representative conceptions by elaborating on the key elements of prostaglandin subsystems and the biochemistry of their various metabolites. This research provided the basis for developing new therapeutic agents for such complications as thrombosis, inflammation and allergic reactions. Once more, an object system was

painstakingly and methodically analyzed into subsystem components, sub-subsystem components, and so on, until a complete explanation of total system dynamics emerged. With regard to his conceptual system, he used six sections, nine figures, and one table in his presentation. He further used between 6 and 14 chemical reaction representations with an average of eight reactions throughout the set. What appears to be implicit in these systems representations is again the constraint of cognitive limitations, which constrain analysis to about seven chunks, versus completeness of representation of key system components. That is, a typically large number of factors must be summarized and abstracted so that only about seven items serve to represent the entire complex phenomenon. Humans can process only about seven items in their short-term memory. Accordingly, a case for the development of a systems template to explain and guide scientific research seems to be further supported. Again, this systems template must consist of only seven or so subsections to be manageable.

Barbara McClintock was awarded the Nobel Laureate in 1983 for her discovery of genome responses to challenge. She analyzed mobile genetic control elements that alter adjacent genes and subsequently alter the function of their associated chromosomes. While her discovery was partially drowned out by the Watson-Crick discovery of DNA genetic information structures, new tools eventually made it possible to verify the existence and action of genetic control elements. She had to fight against a strong scientific consensus that stood in opposition to her findings. She conducted especially intense laboratory analyses for over five decades to confirm and reconfirm her findings. Her research conclusions were finally accepted, as more and more data about genome responses to challenge became available. She had discovered a key genome system control dynamic. Her presentation consisted of seven sections: (1) an introduction, (2) an experiment, (3) effect of x-rays on chromosomes, (4) the telophase nucleus mechanism,

(5) entry of ruptured chromosome end into telophase nuclei, (6) further examples of stressed genomes, and (7) conclusion. Both her representational model and the genome response mechanism are highly systematic in terms of their breadth, depth and internal and environmental dynamics. Here too, a systems and subsystems mapping is appropriate.

Niels Jerne presented "The Generative Grammar of the Immune System" in 1984. He was ingenious in his interdisciplinary application of metaphors and analogies, which he derived from linguistics metaphors, to explain the adaptability of the immune system. As language assembles words into new and needed sentences through the use of generative grammar, the immune system mirrors outside invaders and assembles molecules into specific antibodies to fight these alien invaders. Thus, the immune system maintains open-endedness, with nearly infinite permutation possibilities, to assemble needed antibody configurations. The body apparently possesses a repertoire of innate, deep structures to facilitate the formation of these antibody structures, thus reflecting billions of years of evolutionary history. Jerne's research is particularly imaginative and creative because it reflected the effective and systematic production of significant scientific findings. Further, Jerne broke away from the limitations of two-dimensional representations of antibodies and antigens.

CONCLUSION

This chapter further explores the Laureate cases presented in Chapter 2 against an emergent systems hypothesis of the discovery process. That is, the 20 cases, upon reexamination, reveals that Nobel Laureates possess a keen ability to analyze phenomena through the use of highly systematic frameworks. These frameworks included approximately seven subsystem components. These subsystem components are subtly embedded in the Laureates' sectioning of their respective autobiographical discovery

narratives. The Laureates additionally used illustrations or tables to represent the graphic or numerical side of their discoveries. These tables or illustrations also tended to be limited in each account to some cognitively manageable number of about seven items. Also, each table or illustration typically represented a subsystem facet of the aggregate system that had been discovered. For example, von Behring gave a complete picture of systematic relations between diphtheria and the lymphatic system of an infected host, and the establishment of immune reactions through serum inoculation. Laveran likewise investigated marsh fevers among organisms that hosted the protozoa vector organism and the resultant dynamics of disease etiology; his systems picture was then generalized to a bigger picture involving *Trypanosomes* and a quite broad array of diseases. Carrel developed a systematic, replicable set of procedures to suture blood vessels for organ transplantation. Einthoven's systematic representation of the electrodynamics of the heart led to development of the electrocardiogram. Nicolle reported on the typhus systems cycle and the instrumental role of the louse as a system. Hopkins cast aside prevailing and fallacious theoretical explanations of nutrition and developed an accurate, coherent and systematic picture of growth vitamins and other nutrients. Minot formalized a metabolic picture of nutritional deficiencies that resulted in pernicious anemia and its remediation. Henrik Dam likewise remedied the metabolic deficiencies of vitamins A and D to discover the role of vitamin K in blood clotting. In his discovery of the lethal impact of mold on bacteria, Fleming used an input-output systems model that eventually paved the way for the discovery of penicillin. Theiler studied the impact of serums at the cellular, organ and organism levels of mice to develop an optimal serum dose for inoculation against yellow fever.

Khorana studied nucleic acid synthesis and developed techniques essential to the discovery of the genetic code, clearly delineating a representation of systems thinking in

his account that consisted of a nicely manageable six sections. Hershey and colleagues derived a systems template from the study of DNA structures. Sutherland represented the underlying molecular mechanism of hormones' impact at the cellular level. Edelman produced a systematic, three-dimensional representation of immunoglobulin G and other arrays of antibody structures. Dulbecco and colleagues explained the role of the provirus, how it penetrated cells and produced mutations, and eventually produced cancer. Samuelsson developed highly complex sets of systems representations to explain the actions of prostaglandins. McClintock explained how entire genomic systems respond to challenge. Jerne discovered that antibodies permute to counter invaders in ways that resemble the generation of linguistic grammars.

In conclusion, a set of General Systems Theory categorizations, a systems ontology, emerged from this chapter's analysis. This ontology is evidenced several ways: through the verbal and graphic representation of cellular, organ and organisms and their normal and pathological functioning; through the subdivision of discovery lectures, tables and figures into a limited number of components; and through the close correspondence between discovery representation components and the subsystem components of General Systems Theory. The next chapter attempts to map a General Systems ontology onto various Nobel discoveries, and conversely, to develop a "systems template" that can be used to analyze or prompt discovery. Ultimately, three-dimensional systems templates might well be developed to stimulate and guide scientific research.

Chapter 4: A General Systems Ontology of Nobel Laureate Discovery Patterns

INTRODUCTION

The previous chapter conducted an exploratory survey of a number of Nobel lectures and revealed several salient points. First, all speeches were based on sets of systematic anatomical, physiological and biochemical relationships. Second, there was a surprising consistency in the limited number of sections of each Nobel Laureate speech, with an average of approximately seven sections per speech. This limited number of sections indicates that the discovery process itself appears to be represented in accordance with the limitations of human short-term memory. That is, there is a reasonably close correspondence between these seven section representations and G. A. Miller's classical notion of "The Magical Number Seven Plus or Minus Two: Some Limits on Our Capacity for Processing Information," as the working limits of human short term memory (G. A. Miller, 1956). This limit implies that Laureates must abstract and compress all their findings into seven or so informationally rich chunks, and order the chunks appropriately to configure and represent a discovery (G. Harmon, 1973).

This chapter attempts to map various Nobel discovery accounts onto J. G. Miller's General Systems Theory ontology categories (1995). Miller's ontology portrays living systems in terms of eight unique matter-energy subsystems, and 10 unique subsystems that process information. Additionally, Miller designates two subsystems that process both matter-energy and information. This ontology is represented in the General Systems Ontology section.

This chapter also explores relationships between several Nobel Laureate differentiations used to section off their respective presentations consisting of about

seven sections each, and J. G. Miller's ontology of either eight matter-energy subsystems, or 10 information processing subsystems, plus two common subsystems. Collectively, these subsystems may be used to represent systems structures, functions, and processes at the cellular, organ, and organism levels, as well as their overlapping areas.

This chapter first presents Miller's ontology and reanalyzes selected, previously reviewed Laureate discovery patterns, as well as additional cases. The chapter concludes by proposing that—since most Nobel discoveries seem essentially to be re-conceptualizations of systems phenomena at the cellular, organ and organism levels—a "discovery template" might well be developed to guide ongoing discovery efforts, or to explain past discoveries. This discovery template is based on J. G. Miller's General Systems ontology and G. A. Miller's notion of seven plus or minus two components of human short-term memory.

THE INFLUENCE OF SHORT-TERM MEMORY LIMITS ON NOBEL LAUREATE DISCOVERIES

During this investigation it was repeatedly observed that Nobel Laureate discovery accounts appeared to contain a limited number of subsections. This observation prompted the investigator to review those Laureate accounts that were sectioned off as opposed to those that ran as continuous text. From 1931 through 1990, 62 Nobel Laureate accounts can each be found to incorporate distinct set of sections, ranging from 2 to 16. Most of these Laureate accounts contain about five to nine sections. That is, Laureates tend to explain their discoveries in terms of research phases and systems dynamics at the cellular, organ or organism level, and these explanations appear to be limited by the constraints of human short-term or working memory. This observation led this investigator to conduct a statistical analysis of all discoveries in the 1901–1990 set that were subdivided into substantive sections. Sixty-two sectioned cases were identified,

starting with Warburg (1931), who had 11 sections, through Murray (1990), who had nine sections in his account. For example, the first 10 Laureate discovery accounts are listed below (the full listing is contained in Appendix D):

Year	Laureate	# of sections
1931	Warburg	11
1933	Morgan	4
1944	Erlanger	7
1950	Reichstein	4
1950	Hench	4
1952	Waksman	11
1953	Krebs	8
1953	Lipmann	5
1955	Theorell	5
1957	Bovet	6

It was hypothesized that the 62 cases would have an average number of about seven sections (reasoning from G. A. Miller's "Magical Number Seven Plus or Minus Two"). Thus, it was hypothesized for an independent *t*-test that Laureates tend to organize their presentations into seven sections, and that there would be no significant difference from the hypothetical mean of seven. This can be expressed as a null hypothesis ($H_0 = 7$). The alternate hypothesis ($H_1 \neq 7$) would indicate that the mean number of sections was significantly less or greater than seven. Data follows:

COMPARISON OF ACTUAL AND HYPOTHETICAL MEANS: T-TEST

Number of cases: $N = 62$

Range: 2 to 16

Actual Mean: 7.1

Hypothetical Mean: 7.0

Difference: 0.10

95% confidence interval of difference is: from –0.62 to 0.82

Intermediate values used in the calculation:

$t = 0.2685$

$df = 61$

Standard Error of Difference = 0.360

Results:

Mean: 7.10

DF: 2.84

Standard Error of the Mean: 0.36

$N = 62$

Thus, the null hypothesis of no significant difference between the hypothetical mean of 7.0 and the actual mean of 7.1 is confirmed and the alternate hypothesis can be rejected. There is a remarkable similarity between G. A. Miller's number seven and the mean of sections in 62 Nobel Laureate presentations.

This finding was somewhat of a surprise to this investigator, especially because J. G. Miller's systems ontology features seven levels of analysis, eight subsystems that process matter-energy, and 10 subsystems that process information. The apparent

relationship between the subsystems in Miller's systems ontology and Laureates' sectioning as systems dynamics is explored in General Systems Ontology section of this chapter that follows.

A calculation of the Standard Deviation, Mean and Median was also performed on the number of sections in the same 62 Laureate discovery accounts with the following results:

SECTIONING OF 62 LAUREATE SPEECHES: MEAN, MEDIAN, RANGE AND STANDARD DEVIATION

Number of cases: $N = 62$

Range: 2 to 16

Mean: 7.10

95% confidence interval for actual Mean: 6.376 through 7.818

Standard Deviation: 2.84

Median: 7.00

Average Deviation from Median: 2.19

Again, the dataset is contained in Appendix D.

The above Standard Deviation calculation indicates that about 68% of the number of sections in the 62 Nobel Laureate discovery accounts ranges from 6.376 through 7.818 sections. The number of sections in nearly all (95%) of the Laureate discovery accounts ranges between 1.42 sections to 12.78 sections, which encompasses two Standard Deviations each side of the Mean of 7.10. This Mean of 7.10 with a Standard Deviation of 2.84 is somewhat close to G. A. Miller's "Magical Number Seven Plus or Minus Two." Moreover, the Median is exactly 7.00, and the Average Deviation from the Median is 2.19, which are quite remarkably close to G. A. Miller's "Magical Number

Seven Plus or Minus Two." Interestingly, the median is often regarded as a better representation of central tendency than its corresponding mean, since the median is unaffected by extreme scores or distribution skewness. The influence of memory limits can seen also in the numbers of basic illustrations, tables or figures, that Laureates tend to include their speeches. In Chapters 2 and 3, the numbers of *basic* illustrations for seven Laureates were presented. Einthoven presented six basic illustrations and 19 electro-mechanical or cardiogram illustrations that elaborated on the six basic illustrations. Basic illustration for the other Laureates numbered as follows: Dam (5); Fleming (6); Florey (7); Chain (5); Khorana (7); Samuelsson (9). For the seven Laureates, a total of 45 illustrations were presented, the range is 5 to 9, and the Mean is nearly 6.43 basic illustrations per Laureate. Further, Samuelsson used eight sets of organic chemical illustrations. The eight sets contained, respectively, 6, 6, 6, 9, 6, 7, 10, and 14 reactions (a Mean of 8.00). These Means of 6.43 basic illustrations and 8.00 chemical reactions per set also show the apparent influence of working memory limits. Quite clearly, the Nobel Laureates tend to cognize their discoveries into about seven mental chunks, in accordance with human short-term memory limits, and section off their autobiographical discovery accounts accordingly. This is a major finding of this investigation.

Throughout this study, the Laureates' analytical capabilities appear to be constrained to dealing with about seven chunks, at any given time, throughout their abstraction and analytical processing. From the study of specific discovery accounts in this study, short-term (working) memory limitations appear to impact Laureate research in the following manner: (1) the scientists tended periodically to summarize or abstract their laboratory or field findings into multiple chunks or categories; (2) when the number of abstracted chunks exceeded their short-term memory limits, they would reduce the number to a cognitively manageable seven chunks by summarizing further to

successively higher levels of abstraction; (3) eventually, the set of findings would be abstracted into about seven very informationally rich chunks, and these rich chunks, when appropriately ordered, would represent their discoveries. These Laureate discoveries, then, consist of conceptual system representations of some natural, object process or system at the cellular, organ or organism level. Conversely, on the cognitive input side, cellular, organ or organism subsystems can all be mentally represented as a set of informational chunks.

The subsystem ontologies of General Systems Theory (Appendix C) can be used as fairly complete templates to map the represented cellular, organ or organism components and processes. These ontologies could be applied to suggest to researchers which parts of subsystems or systems under investigation require further study. Hence, information needs can arise periodically during the conduct of research. Incongruent or missing parts or processes can be sought or investigated, and subsystems harmonized with one another, until a complete, coherent systems model is developed.

The influence of short-term memory limits in Laureate discovery appears to be significant because these limits rather severely constrain each scientist's analytical capability. If Laureates can afford to cognize only about seven basic information chunks during the discovery process, they must repeatedly condense, weed and reorganize, eventually developing chunks that are more complex and informationally rich. Laureate discovery representations are abstract, and their components or parts must likewise be abstract. That is, Laureates must convert pennies to silver dollars, so to speak, and then order these silver dollars appropriately, to culminate their research efforts (G. Harmon, 1973).

However, since G. A. Miller's 1956 paper on "The Magical Number Seven" was published other psychologists have challenged the concept that the true span of human

short-term memory is different from seven. Therefore, the following section reviews more recent thinking about the limits of short-term memory.

CONTEMPORARY THINKING ABOUT SHORT-TERM MEMORY LIMITS

Given that Nobel Laureates tend to organize their discovery accounts into about seven substantive sections, it is interesting to probe further why they have done so, and done so consistently, over a period of nearly six decades. It appears that these scientists were immersed for years in their respective specialized domains of inquiry. From their accounts, these scientists all tend to be highly motivated and driven individuals who are relentless in their quest to understand the secrets of nature. There is little question that they have achieved an in-depth, gestalt view of their specialized areas of medicine and physiology. There is also little question about their use of rigor and creativity in attacking research problems. These scientists display excellent long-term memory of their cumulative research, as evidenced by their use of recorded knowledge and citation patterns of other scientists and their own works. They possess a storehouse of foundational working knowledge. Additionally, these scientists are able to display highly effective, short-term working memories, as evidenced by their propensity to organize and present research through the economical sectioning of their abstract research accounts, and through the apt use of illustrations, figures and tables.

Nevertheless, there has been some disagreement among psychologists as to the number of cognitive chunks that can be processed in working memory at any given time (Cowan, 2001). Estimates of short-term memory span have varied recently from about three to nine chunks, resulting in somewhat of a challenge to G. A. Miller's estimate of seven plus or minus two. But Baddeley (1994) reexamined Miller's classical, 1956 "Magical number seven…" article and found Miller's assertions to be reasonably accurate and remarkably timeless. Also, older dichotomies between short- and long-term

memory have been weakened as a more integrated perspective provides for a continuum of interactions between short- and long-term memory. In a masterful synthesis of research on human memory, Baddeley (1999, pp. 19, 41, 106, 324) provided insights that help explain the facets of Nobel Laureate working memories and their rather consistent tendency to report findings in roughly seven chunks. Memory appears to be not a single system, but an array of dynamically interacting systems. Long-term memory appears to have slow input and retrieval, but high, durable storage capacity, especially for semantic content, whereas, short-term memory is capable of rapid input and retrieval, but possesses low capacity and is used for temporary storage and the permutation of chunks retrieved from long-term memory or perceived as a result of observation. When chunks processed are more language-like and meaningful, the span of short-term memory appears to increase from lower to higher limits. Short-term memory is thus largely responsible for retrieving and manipulating information. Chunks may take the form of larger schemata, which are internal representations or models of an individual's knowledge, and which are used to encode and store new information. The study of memory is becoming increasingly multidisciplinary, dynamic and related to contextual domains.

The tendency of Laureates to use seven sections can be viewed from other perspectives besides memory span limitations. Medin, Lynch and Solomon (Medin *et al.*, 2000) asked, "Are There Kinds of Concepts?" and provided a thorough review of contemporary perspectives on this topic in *The Annual Review of Psychology*. Concepts may be differentiated according to their structural differences, processing differences and content-laden principles. Concepts may be further differentiated according to structure: nouns versus verbs; isolated versus interrelated concepts; objects versus mental events; artifacts versus natural kinds; abstract versus concrete; basic level versus subordinate and

super-ordinate concepts; hierarchies versus paradigms; category structures versus brain anatomy. Additionally, concepts may be based on different kinds of mental processing: common taxonomic versus goal-derived categories; social versus individualized processing; stereotypes, subtypes, and subgroups. Apparently, then, an analysis of Laureate research patterns can incorporate not only memory phenomena, but also the study of conceptualization and other cognitive phenomena as well. Last, it can be observed that Laureates all deal with recorded knowledge and abstract concepts over extended periods of time within authentic laboratory or field settings. Such characteristics of Laureate research seem to support the case that their working memory limitations are less restrictive than the memory limitations of experimental psychological subjects assigned to recall or manipulate randomized digits, sounds, colors or nonsense syllables in contrived, experimentally regulated settings.

The following section on General Systems Ontology attempts to demonstrate how elements of several Nobel Laureate discoveries can be readily mapped onto systems ontologies or templates (see Appendix C). As stated earlier, these ontologies contain eight unique subsystems that process matter-energy, and 10 unique subsystems that process information at the cellular, organ and organism levels of analysis. Additionally, two subsystems process both matter-energy and information. The 8 and 10 subsystems also reflect the possibility that short-term memory limits have been imposed, to circumscribe and limit these General Systems ontologies. Likewise, the Laureates' sectioning of research accounts into about seven components reflects the possibility of the operation of memory limitations to achieve cognitive manageability. The following ontology illustrations demonstrate how Laureate discovery patterns can be explained through the use of systems and subsystems concepts. Conversely, systems ontologies might be potentially used to prompt and guide the discovery process. By analogy, the

Periodic Table of Chemical Elements has been and still is being used to explore the nature of fundamental elements and interrelate them as parts of a systematic set of elements.

GENERAL SYSTEMS ONTOLOGY

One of the most exhaustive treatments of General Systems Theory is J. G. Miller's classical analysis in his 1102 page work, *Living Systems* (1978). In 1995, Miller published a paperback edition of his earlier work with an original "Preface to the Paperback Edition" (1995, pp. xiii-xxv). This significant preface updated and summarized his thinking about General Systems Theory between 1978 and 1995. In the preface Miller presented a table titled "The 20 Critical Subsystems of a Living System," which applied to all subsystems levels—cellular, organ, organism, group, organization, community, society and supranational system levels. As used here, an ontology may be defined as the outcome of an effort to produce a rigorous and exhaustive conceptual schema, usually of a hierarchical nature, about a given subject domain ("Ontology (computer science)," 2005). The term has been used as such in recent years within computer and information science circles. Miller's 20 Critical Subsystems with his definitions are presented below (1995, p. xix).

Subsystems which process both matter-energy and information:

1. *Reproducer*: The subsystem which carries out the instructions in the genetic information or charter of a system and mobilizes matter, energy, and information to produce one or more similar systems.
2. *Boundary*: The subsystem at the perimeter of a system that holds together the components which make up the system, protects them from

environmental stresses, and excludes or permits entry to various sorts of matter-energy and information.

Subsystems which process matter-energy

3. *Ingestor*: The subsystem which brings matter-energy across the system boundary from the environment.
4. *Distributor*: The subsystem which carries inputs from outside the system or outputs from its subsystems around the system to each component.
5. *Converter*: The subsystem which changes certain inputs to the system into forms more useful for the special processes of that particular system.
6. *Producer*: The subsystem which forms stable associations that endure for significant periods among matter-energy inputs to the system or outputs from its converter, the materials synthesized being for growth, damage repair, or replacement of components of the system, or for providing energy for moving or constituting the system's outputs of products or information markers to its suprasystem.
7. *Matter-energy storage*: The subsystem which places matter or energy at some location in the system, retains it over time, and retrieves it.
8. *Extruder*: The subsystem which transmits matter-energy out of the system in the forms of products or wastes.
9. *Motor*: The subsystem which moves the system or parts of it in relation to part or all of its environment or moves components of its environment in relation to each other.
10. *Supporter*: The subsystem which maintains the proper spatial relationships among components of the system, so that they can interact without weighting each other down or crowding each other.

Subsystems which process information

11. *Input transducer*: The sensory subsystem which brings markers bearing information into the system, changing them to other matter-energy forms suitable for transmission within it.
12. *Internal transducer*: The sensory subsystem which receives, from subsystems or components within the system, markers bearing information about significant alterations in those subsystems or components, changing them to other matter-energy forms of a sort which can be transmitted within it.
13. *Channel and net*: The subsystem composed of a single route in physical space, or multiple interconnected routes, over which markers bearing information are transmitted to all parts of the system.
14. *Timer*: The subsystem which transmits to the decider information about time-related states of the environment or of components of the system. This information signals the decider of the system or deciders of subsystems to start, stop, alter the rate, or advance or delay the phase of one or more of the system's processes, thus coordinating them in time.
15. *Decoder*: The subsystem which alters the code of information input to it through the input transducer or internal transducer into a "private" code that can be used internally by the system.
16. *Associator*: The subsystem which carries out the first stage of the learning process, forming enduring associations among items of information in the system.

17. *Memory*: The subsystem which carries out the second stage of the learning process, storing information in the system for different periods of time, and then retrieving it.
18. *Decider*: The executive system which receives information inputs from all other subsystems and transmits to them information outputs for guidance, coordination, and control of the system.
19. *Encoder*: The subsystem which alters the code of information input to it from other information processing subsystems, from a "private" code used internally by the system into a "public" code which can be interpreted by other systems in its environment.
20. *Output transducer*: The subsystem which puts out markers bearing information from the system, changing markers within the system into other matter-energy forms which can be transmitted over channels in the systems's environment.

Again, it can be noted that there are eight distinctive subsystems, which process matter-energy, and 10 distinctive subsystems, which process information. These numbers appear to be significant here because the numbers are close to the classical seven plus or minus two, and because Laureates tend to use seven sections to represent their discoveries in their acceptance speeches. These observations appear to be significant enough to justify the development of a General Systems ontology or template to represent and explain Laureate discovery patterns better and perhaps, eventually, to facilitate future scientific inquiry. After all, most Laureates, when they make a discovery, tend to conceive of a new system, or a subsystem thereof, or to re-conceptualize a previous systems concept. Within the first Nobel century of medicine and physiology discoveries (from 1901 through 1990), this investigator found that the Laureates' re-conceptualizations or original

conceptualizations have prevailed most frequently at the cellular level, secondly at the organ level, and thirdly at the organism levels of analysis. Systems concepts also apply in Laureate explanations of surgical procedures, community-wide epidemiological processes, or the development of the electrocardiogram or computerized axial tomography.

The following sections elaborate on both early and more recent previously reviewed discoveries, all of which involved critical subsystems and processes at the cellular, organ, and organism levels. The analysis is extended to additional cases for illustrative purposes. The role of human short-term memory limits in these discoveries is also reflected in the following discovery representations.

REANALYSIS OF CASES VIA SUBSYSTEM CATEGORIES

This section further analyzes the cases presented in Chapters 2 and 3 through the use of J. G. Miller's cellular, organ and organism subsystem categories. The purpose here is to discern the degree to which the key cellular, organ or organism concepts presented in each case are commensurable with Miller's corresponding subsystem categories. The concept of a discovery template also is further discussed. To make these case-subsystem comparisons, this investigator coded the key concepts from each Laureate's account into blank worksheets containing J. G. Miller's subsystem category labels (see General Systems Ontology Worksheets, Appendix C). This approach provided a practical method of testing the degree to which the Laureate's mapping of concepts corresponded with Miller's subsystems mappings. Miller's subsystem categories are represented in **bold** font in the following comparisons.

Von Behring (1901)

A re-visitation of von Behring's Nobel lecture reveals several parallels between his analysis and J.G. Miller's subsystem categories:

> The way in which the diphtheria bacilli after penetrating into the human body, release their poison and how this poison develops its destructive activity has been the subject of many interesting investigations…. diphtheria bacilli are first localized in the pharyngeal amygdala, which, in all probability, they reach principally via the breath, but also in substances which we take in by way of nourishment. In the niches and small cavities of the amygdala the diphtheria bacilli can multiply as though in an artificial incubator and excrete their poisons…. The diphtheria poison gets into the blood stream by way of the lymphatic vessels and starts up inflammatory processes from there in the various organs. The inflammatory symptoms are outwardly visible chiefly in the proximity of the site of production, on the pharyngeal mucous membrane and in the larynx. (von Behring, 1967, pp. 6-7)

Von Behring's account of the spread of human contagion and development of diphtheria corresponds closely with J.G. Miller's description of matter-energy subsystems, particularly at the organ level (J. G. Miller, 1995, p. 323). In Miller's subsystems terminology, diphtheria bacteria transgress the **boundaries** of outer layers of coverings of organs, that is, mucous membranes of mouth and nose, walls of lymphatic vessels. The bacteria then progress through **ingestors,** lymphatic vessels, nose and mouth, alveolar capillaries in the lung, lacteal lymphatic capillaries in the wall of the intestine, and other parts of the gastrointestinal tract. Blood vessels, lymphatics, organ ducts and intercellular fluids **distribute** the bacteria and their toxins. All cells of the organs, especially parenchymal cells, convert (**converter**) the matter-energy as infection spreads, and serve as **producers** of more bacteria and toxins. Intercellular fluids and hollow cavities of organ components, in Miller's terms, provide **matter-energy storage**. Lymphatic and venous output vessels, ducts and other openings and glandular drainage all serve as **extruders**. Collectively, most organs and tissues of the body provide **motor** functions to transport infection, while stroma, walls, connective tissues of organ

components provide overall **supporter** functions. Von Behring also developed his diphtheria immunization approach and used similar systems concepts (boundary crossing vaccine injections, which were ingested and distributed throughout the body). Overall, there appears to be a close correspondence between von Behring's 1901 description and Miller's 1995 description of organ subsystems. This correspondence supports this investigator's case for the use of a discovery template to facilitate the analysis of such discoveries.

Laveran (1907)

A review of Laveran's discovery of protozoa as a cause of marsh fevers, particularly malaria, reveals a pattern of correspondence to subsystem concepts similar to that in the analysis of von Behring's case above. Laveran was recognized for discovering that protozoa entered the skin **boundaries** of humans, were **ingested** and **distributed** via blood plasma, entered the boundaries of red blood cell walls, eventually, **converting** red blood cell components into black particles called melanins. Thus, the blood and other organs served the additional functions of **production**, and **reproduction** as well as **matter-energy** storage. The entire human organism and its organ subsystems fulfilled **motor** and **supporter** functions, while mucous membrane waste output served **extruder** functions. Therefore, all 10 of Miller's subsystem typology, especially at the organ level, served as a basis for reinterpretation of Laveran's investigation in systems ontology.

But such reinterpretations require some degree of subjective categorization on the part of the interpreter doing the analysis. As a cautionary note, the subsystem template merely serves as a loose heuristic device for analysis and interpretation of disease states and their underlying etiology. It is probably necessary for those who would attempt to deploy subsystem categorizations to analyze scientific findings to acquire a reasonable

amount of case-by-case training and experience to produce scientifically valid and reliable results.

Carrel (1912)

Carrel developed a method to suture blood vessels and reestablish healthy circulation, thus enabling surgeons to replace diseased organs with healthy ones, or to reattach a detached limb or graft a new limb onto a patient. At first glance, Carrel's work appears to be somewhat mechanical and not amenable to subsystem categorization. Upon further analysis, though, the vascular subsystem may be analyzed at the organ subsystem level. Referring again to Miller's organ subsystem chart (1995, p. 223), the blood vessel walls comprise a set of **boundaries**, while the blood vessels serve as **distributors** and **ingestors** (input arteries or portal vein of liver). The bone marrow and blood themselves serve **producer**, **converter** and **matter-energy storage** functions through the **production** and **transport** of blood cells and other components. Certain venous vessels and renal veins, in Miller's categorization, fulfill **extruder** or output vein functions. The **supporter** function is fulfilled through vascular connective tissues, organ components and, most importantly, through sutures. Miller even explicitly uses the addition of a prostheses or artificial limbs to illustrate the **motor** function in his subsystem categorization. Obviously, the heart pumps blood and also fulfills a **motor** function. At the organ level of subsystem analysis, Miller does not address the **reproducer** function, although, bone marrow and blood components are instrumental in **reproductive** functions and blood vessels can redevelop. Carrel's discovery, then, does appear to lend itself to a Systems Theory reinterpretation and to systems-driven analysis. All nine of Miller's **matter-energy** subsystems at the organ level can be reasonably superimposed onto Carrel's account of his successful suturing and transplanting discoveries.

Einthoven (1924)

Einthoven developed the string galvanometer to measure action currents of the heart and to diagnose various cardiac diseases and conditions. This investigator was surprised to find that Miller, somewhat like Einthoven, diagrams the heart and specifies the subsystem functions for the heart, primarily at the information processing level and secondarily at the matter-energy level (J. G. Miller, 1995, pp. 322-323). Information processing components include the **input transducer,** postsynaptic region of autonomic postganglionic neuron; **internal transducer,** cardiac muscle cells which signal denervated organs to contract; **channel and net,** autonomic nerve plexus of heart and large blood vessels and parts of the cardiac muscle that elicit contractions; **decoder,** postsynaptic region of autonomic postganglionic neuron; **decider,** Purkinje fibers, sympathetic fibers of sinoatrial node, bundle branches and atrioventricular bundle; **encoder,** presynaptic area of heart output neuron; and **output transducer,** presynaptic area of heart output neuron. J. G. Miller (1995, pp. xxii, 341) also summarizes the pacemaker function as the **timer** component of the heart; the Purkinje fibers initiate and conduct pulses through the myocardium, while the sinoatrial node has been regarded as the focus in the mammalian heart–the origin point of heart beats. Miller notes that at the organ level the **associator** and **memory** functions have not been fully identified. Accordingly, Miller identifies eight information processing subsystem components at the heart organ level and discusses a few matter-energy subsystem components.

Einthoven referred indirectly to the above subsystem components when he developed various related electrocardiogram diagnoses: the normal heart beat; Stokes-Adams disease with left ventricular hypertrophy; premature contractions of the heart (premature systoles and extra systoles); blocks in the left branch of the bundle of His. While Einthoven did not study a wide variation of heart diseases while developing the

string galvanometer, he and his successors did go on to further develop electrocardiogram technology and to measure the characteristics of a wide array of heart disorders and diseases.

The above four cases serve to illustrate correspondences between the Nobel Laureate discoveries and General Systems ontologies at the organ, organism and cellular levels. But all four speeches were written as continuous text rather than as sectioned presentations. For the first half century of Nobel Laureates in Physiology or Medicine, it was customary to present treatises as continuous text, many of which were not footnoted and not otherwise standardized with regard to writing form and style. In the 1960s, however, Nobel Laureate speech texts began to be presented in sections, and incorporated a more formal academic writing style with stricter adherence to citation of references.

The next four analyses involve another review of cases addressed earlier, but each one contains about seven subsections, and continue to present explorations of parallels between Nobel discoveries and Miller's general subsystems categories. The following analyses also explore the cognitive chunking of Nobel scientist thinking into cognitively manageable components. The restricted number of these components in each case appears to accord with the limitations of working human short-term memory, seven plus or minus two. The cases thus serve to illustrate the possibly feasible use of a discovery template based on both systems theory categorizations and short-term memory limits.

Khorana (1968)

What is remarkable about Khorana's synthesis of nucleic acid and clarification of the genetic code is that his lecture contained six sections, seven figures, and eight tables, categorizations that reflect short-term memory limitations. The six sections include: (1) an introductory review of earlier genetic research centered on DNA and RNA structures; (2) polynucleotide synthesis and the genetic code; (3) polypeptide synthesis and the

genetic code; (4) transfer RNA structures; (5) an elaboration of code and protein synthesis; and (6) an overall conclusion that explained how the problem of the genetic code had been partially resolved in a one-dimensional sense. Khorana's tables deal with complex sequencing and genetic code illustrations, while his figures generally illustrate the time dynamics and structural aspects of protein synthesis. In systems terms, Khorana conducted his research at both the matter-energy and the information processing cellular levels (J. G. Miller, 1995, pp. xx-xxiii, 219). He deals with nine subsystem categories: the genes of parent cells (**reproducer**); cellular **boundaries** in polynucleotide and polypeptide synthesis; **internal transduction** in the process of synthesis; RNA and DNA structures (**channels and nets**); molecular binding sites (**decoder**); binding sites for transfer and activator RNA (**decider**); genes that specify hormones (**encoder**); various forms of protein synthesis (**producer**); and protein structures (**supporter**). Again, nine subsystem categories appear to be commensurable with Khorana's account of his nucleic acid synthesis and genetic code discoveries.

Each of his six sections seem to reflect the above subsystem categorizations, while his eight tables illustrate aspects of **internal transduction**, **encoding**, **decoding**, and **conversion**. His seven figures represent the details of protein synthesis vis-á-vis **transduction**, **conversion**, and so on. His six sections demonstrate Khorana's discovery pattern and the interplay of short-term memory limitations, which were largely guided by systems pattern building and refinement. Apparently, to make the overall task cognitively manageable, Khorana subdivided his task into orderly, cognitively manageable phases. Again, section one provided a history of previous efforts to understand the genetic code and served as and provided a rudimentary understanding or systems platform for Khorana's research. Section two dealt with the sub-processes of polynucleotide synthesis. Likewise, section three presents the elements of polypeptide synthesis, while section four

illustrated the structural dynamics of Transfer RNA. Section five elaborated on additional aspects of the genetic code and protein synthesis, and section six furnished a picture of the general structure of the genetic code. By and large, his discovery was based on a block building approach that culminated in a complete, systematic model of the genetic code and how its nucleic acid components are synthesized. Perhaps a systems ontology might have served Khorana by prompting and guiding him through a painstaking, 10-year inductive effort. The limits of this scientist's working memory seem to be apparent throughout his entire account. The overall problem had to be broken down into manageable sequential phases.

Edelman (1972)

Edelman made his contribution by discovering the nature of antibody structures and its' role in molecular immunology. His Nobel lecture consists of six major sections: (1) the multi-chain structure of antibodies; (2) the covalent structure and domain hypothesis; (3) the evolution of gene duplication and immunoglobulin classes (translocons); (4) lectin stimulation of lymphocytes; (5) antibodies on antigen-binding cells; and (6) a conclusion consisting of five key points. It is worthwhile to note that these six sections can be superimposed onto Miller's subsystem categories across the board. Edelman was concerned with gene duplication or **reproduction** and **production**; overall **structure** or **supporter** functions; stimulation of lymphocytes and other cells, or **transduction** and c**onversion**; and conclusions dealing primarily with antibody classes and structures and their roles in immunology. More specifically, Edelman appears to have focused most heavily on the multi-chain structure of immunoglobulin antibodies and the **ingestor** functions whereby antibodies engulf antigens. Remarkably, the central dogma of modern immunology was concerned with the **decider** function, whereby molecular recognition of antigens occurs by selection among clones of cells of different specificity

already committed to appropriate antibody production. Moreover, Edelman capitalized on the recognition of previously discovered Bence Jones proteins, a byproduct apparently secreted by myeloma tumors. Bence Jones proteins then are excreted into urine of the tumor host (**extruder** function). A truly rigorous analysis of Edelman's account requires expertise beyond that possessed by this investigator, but there are some remarkable parallels between J. G. Miller's subsystems frameworks and Edelman's six-part lecture and five-point conclusion. That is, there is support here for the notion that investigations and discoveries are necessarily limited by the severe constraints of human short-term memory. Both Miller (1995) and Edelman utilize categorizations consisting of 6 to 10 chunks or components. Hence, the case for deployment of a discovery template for discovery analysis is further confirmed.

Dulbecco (1975)

As pointed out in Chapter 2, Dulbecco's account of his discovery was especially notable because it offered a complete, systematic picture of discovery neatly grouped into seven components. His seven-component system might serve as an example of a discovery or research template that could be used to characterize or guide research endeavor. He even included a simple six-point summary of his discovery in his introductory section, which again reflects the cognitive constraints. Dulbecco was recognized in 1975 for his discovery that demonstrated how normal cells are transformed into cancer cells through exposure to radiation, chemicals, or tumor viruses. His seven part lecture consisted of an overview of the provirus; transformations of the virus; the viral transforming protein; cellular dynamics in transformation; cellular mutations; cancer prevention prospects; oncogenic substances, environmental pollution and social reform. Many subsystem concepts are implicitly expressed in the text of Dulbecco's quite readable lecture. At the matter-energy level, he discusses cell **boundaries**; cell **ingestion**

of provirus entities through cell **boundaries;** protein **conversion** and **transformation;** cellular DNA for **matter-energy storage;** and the overall **supporter** functions of the cellular cytoskeleton. At the information processing level, he concerns himself with **input** and **internal transduction** of DNA, **decoding** through molecular binding sites, and the **encoding** of oncogenes. Overall, Dulbecco offers somewhat of a textbook case of integrating findings into a clear, manageable structure of useful knowledge. More than other Nobel Laureates, he masterfully weaved the research of others into his investigations and report of findings.

Samuelsson (1982)

Bengt Samuelsson studied the biochemical mechanisms and biological mediators, including prostaglandins and leukotrienes. His account is notable because his organic chemical illustrations include, respectively, 6, 6, 6, 9, 6, 7, 10, and 14 chemical reactions, an average of eight through the set. It seems apparent that some chemical reactions might best be presented elegantly and economically through simplified illustrations that contain roughly seven components. Likewise, a chemical template to guide biochemical reaction research might effectively support the discovery process.

One of the most popular accounts in the history of science has to do with how the Periodic Table of Chemical Elements, when first conceived, reflected many missing elements in the matrix which inspired investigators to discover those missing elements and to plug them into their respective spots. Samuelsson's illustrations refer to **transformation** and aggregation processes in human platelets; interaction between platelets and the vessel **supporter** wall; formation or **production** of leukotrienes, prostaglandins, and thromboxanes. The analysis of this case is quite difficult for the lay investigator because it requires a sophisticated knowledge of biochemistry, and

recognition of interrelations between Samuelsson's equations and Miller's subsystem categories may not be readily apparent.

ANALYSIS OF ADDITIONAL CASES VIA SUBSYSTEM CATEGORIES

The above analysis of eight cases is a revisitation of Laureate speeches reviewed initially in Chapter 2 and analyzed in their broader dimensions in Chapter 3. In this chapter, the investigator attempts to point out similarities between Laureate research categorizations as presented in their Nobel Lectures, and the matter-energy and information processing categorizations of subsystems developed by systems theorist J. G. Miller. Several close parallels or mappings between these two sets of categorizations have been noted. The procrustean limitations of human short-term memory and its constrained operation seem to be readily apparent. Both the Laureates and Miller tended to restrict their analyses to approximately seven basic categorizations. To further cross check the validity and reliability of these observations, summaries of two new case analyses are presented below. Ross (1902) centered on the etiology of malaria and is included to represent an earlier time period, while Sperry (1981) represented more recent research on the role of the right cerebral hemisphere in overall cognitive functioning.

Ross (1902)

In 1902 Ronald Ross (1967) was awarded the Nobel Prize for discovering that the *Anopheles* mosquito was the intermediate vector responsible for the transmission of malaria and for subsequently developing methods for destroying mosquitoes. While working earlier as an English Army surgeon in India, Ross deliberated about previous theories on the nature of malaria and earlier hypotheses that mosquitoes were the responsible vectors. In fact, he noted that East African native tribes used the same name for mosquito and malaria. Ross conducted experiments to study the cause of malaria

transmission by using mosquitoes that were newly hatched from larvae in his laboratory. Ross allowed these newly hatched mosquitoes to bite malaria patients and then studied the malaria parasite in the body of these mosquitoes. While these experiments were initially unsuccessful, in 1897 he found foreign bodies in the wall of the stomachs of a less common species of mosquito that appeared to be forming into the human malarial parasite. He also found corresponding parasites for avian malaria in the bodies of mosquitoes and traced the growth of these parasites inside these mosquitoes. Ross found that a process of fecundation initially takes place and leads to the formation of parasites. In turn, the parasites penetrated and embedded themselves in button-like structures in the stomach wall and projected outward into the mosquito body cavity. From these embedded structures, numbers of elongated sporozoites formed and eventually broke out to spread through the entire body cavity of the mosquito, and to accumulate in its salivary glands. Through his laboratory work, he found that the salivary glands were connected with the proboscis, and thus the infliction of mosquito bites infected a human or other host (Mörner, 1967, pp. 23-24).

Because Ross's Lecture is not subdivided and runs as a continuous historical account, it is difficult to discern how he established distinctions between the different major concepts that he presented. In terms of Miller's systems schema for organisms, it may be said that the mosquito had acquired the parasite through its proboscis (**ingestor** subsystem) thus penetrating the mosquito's external boundary (**boundary** subsystem) and entering its stomach (**converter** subsystem), wherein a compatible genetic and nutritional environment existed to support reproduction (**reproducer** subsystem) and growth (**producer** subsystem) in button-like structures. The parasites then multiplied and protruded into the body cavity (**matter-energy storage**) of the host mosquito, which provided a distributor mechanism (**distributor** subsystem) within each mosquito, along

with eventual extrusion (**extruder** subsystem) through the proboscis. The saliva glands also served to store parasites (**matter-energy storage subsystem**) and the movement and biting mechanisms of the mosquito served as **motor** and **supporter** subsystems. In terms of Miller's matter-energy subsystems, it is apparent that Ross provided an explanation that included all eight matter-energy components. Ross thus confirmed his and others' hypotheses about the mosquito as the primary vector for transmitting the malaria parasite, and provided a systematic explanation of parasitic reproduction within the mosquito and extrusion of parasites into other organisms, including humans. Had Ross studied General Systems Theory, he might have been able to conceptualize his resulting discovery earlier and more directly. That is, by having a complete set of subsystem components (**ingestor**, **producer**, **reproducer**, **converter**, **distributor**, **storage**, **extruder**, etc.) before him, the parasitic life cycle within the host mosquito and its subsequent transmission to other organisms might have become apparent more quickly. Sound conceptualization through the analysis of subsystem interdependencies can serve to target laboratory observations at the organism level, including microbiotic organisms. In other words, a systems template might serve to reduce experimental trial-and-error and thus accelerate discovery.

Sperry (1981)

Roger Sperry(1993) investigated the effects of disconnecting the left and right cerebral hemispheres and elaborated on the importance of the right cerebral hemisphere, which previously had been considered to be an unimportant, mute partner of the left hemisphere. His lecture is subdivided into seven sections: (1) the classical view of cerebral dominance, which held that the left hemisphere was more highly evolved and intellectually superior to the relatively retarded right hemisphere; in contrast, the right hemisphere was held to be agraphic, dyslexic, apraxic, word-deaf, mute, and generally lacking in higher cognitive function; (2) evidence from commissurotomy that

contradicted the classical view and revealed that the right hemisphere was clearly superior to the left in terms of concrete thinking and the apprehension and processing of spatial patterns; (3) an exploration of the right hemisphere language controversy, which Sperry resolved by noting the right hemisphere also possessed the ability to perceive language and complex sounds; (4) right hemispheric specialization, which allows the perception of nondescript patterns and spaces; the appreciation of musical melodies, voices, and tones; and heightened artistic abilities; (5) additional findings that revealed that the two hemispheres do indeed work together as cooperative, proactive partners, and that impulses between the hemispheres may go in up-down, front-back, or sideways directions; (6) self consciousness, social awareness and emotions are all important cognitive functions, and these reside heavily in right hemispheric consciousness; (7) a revised and more holistic interpretation of the mind-brain problem that emphasized unified rather than dichotomous views of consciousness.

In terms of systems theory, Sperry's analysis is compatible with the organism level of analysis. The various sense organs serve as **input** and **internal transducers**. The cerebral hemispheres fulfill the functions of **decoder**, **associator**, **decider**, **encoder** and **memory**, while the motor neurons serve as **output transducers**. More importantly, Sperry re-conceptualized the brain as a complex system of **channels and nets**, wherein the left and right brains collaborate to bring about more complete forms of cognition and consciousness. In other words, Sperry discovered the existence of a highly functional right brain that complemented the strengths and compensated for the weaknesses of the left-brain. As a result of Sperry's investigations, the left and right brains may be viewed as complimentary subsystems of an integrated and super-ordinate cognitive system. The benefit of deploying a systems view in the kind of research that Sperry undertook would appear to be the ability for investigators to grasp more quickly the required gestalt views

of mental functioning and drastically broaden the scope of their analyses to embrace wholes rather than parts. Sperry's seven-part account is also indicative of how short-term cognitive constraints can be imposed on scientific analysis and renditions.

CORRESPONDENCE OF LAUREATE SUBSYSTEMS TO SYSTEMS ONTOLOGY

To summarize the above 10 cases, it can be noted that eight of von Behring's subsystems were matched to J. G. Miller's matter-energy subsystems ontology, which also consists of eight subsystems. Laveran's subsystems representations also fit eight ontology categories as did those of Carrel, Khorana, Edelman, and Ross. Einthoven's 10 subsystems representations fit into all 10 of J. G. Miller's information processing subsystems ontology, while Sperry's representations matched nine of Miller's 10 information processing subsystems categories. The analysis of Dulbecco account produced seven subsystem representations out of eight of Miller's matter-energy subsystems categories. The analysis of Samuelsson's account yielded only three matches to Miller's eight subsystems in the matter-energy ontology.

It can be noted that in nine of the 10 Laureate accounts, their subsystems matched Miller's ontologies very closely or, in six cases, matched completely. A binomial sign test for nine successes out of 10 trials yielded a *two-tail P* value of 0.0215. In the sign test, if the probability of "success" in each trial is 0.500, then the probability of observing either nine or more successes, or one or fewer successes, in 10 trials is 0.215, or 2.15%. The sign test result indicates a very close match between Laureate subsystem representations and their corresponding representations in the General Systems Theory ontology. Here too, the first and major hypothesis of this investigation is supported.

CONCLUSION

The adoption of a General Systems set of categorizations—an ontology—to explain retrospectively the dynamics and patterns of discovery appears to be feasible and can be applied to the analysis of additional discoveries. The components of each discovery can be mapped onto the systems ontology; conversely, the systems ontology could be developed and deployed to facilitate fundamental inquiry or even discovery. The systems ontology consists of either eight unique matter-energy subsystems or 10 unique information processing subsystems. Likewise, a *t*-test that compared the Mean number of sections in 62 Laureate accounts (mean = 7.10) with the classic "Seven Plus or Minus Two" limits human short-term memory (mean = 7.0) revealed no statistically significant difference at the 95% confidence level. The Standard Deviation for the same distribution (Mean = 7.10) is 2.84, indicating that about two-thirds of the number of sections in the Laureates' discovery accounts range from 4.26 to 9.91 sections. Remarkably, the Median for the distribution (n = 62) is exactly 7.00, while the Average Deviation from the Median is 2.19. A calculation of the number of key Laureate illustrations (from seven cases presented in Chapters 2 and 3) yielded a mean of 6.43 illustrations per Laureate. Laureate Samuelsson presented eight sets of organic chemical reactions, with a mean of eight reactions per set. These numbers are strikingly close to G. A. Miller's "Magical Number Seven Plus or Minus Two." Short-term memory limits served to rather severely constrain Laureates' analyses and representations to make them cognitively manageable.

Moreover, the functional components of each Laureate's discovery account appear to correspond with the functional components of the systems ontology at either the matter-energy level or the information processing level of analysis. These close functional and numerical mappings might be also regarded as one of the significant findings of this investigation.

An analysis of recent works on the nature and number of components of human short- and long-term memory reveals considerable interdependency between these two memories. Short-term memory can be limited to between about three and nine chunks. However, in the case of extended, recorded scientific research—of the type that Nobel Laureates undertake—working memory appears to hold about seven components. These components take the form of distinct conceptual entities in scientific research, and recent psychological research suggests that there are multiple kinds of concepts. Because Laureate research can be readily considered to be highly conceptual and abstract, short-term memory limits would appear to be numerically larger than for tasks involving the cognitive processing of numbers and other less abstract symbol sequences.

An underlying theme that runs through the cases analyzed here, and through other Laureate discoveries as well, is that all the scientists tend to re-conceptualize or to elaborate on previous models. That is, Laureates either tend to reject past or prevailing theories of biological processes and disease, or to fill in missing parts of existing conceptualizations. In short, the scientists appear to rely indirectly on a systems model with a limited number of subsystem components.

Although Laureates are not usually explicit about their understanding or use of systems concepts, their discovery accounts map rather nicely onto a General Systems Theory template. A sign test confirmed the close match between Laureate subsystem representations and the Systems templates. In a contrary fashion, a General Systems Theory template (Appendix C) can be readily superimposed onto the rendition of each Nobel Laureate. This chapter accordingly proposes the development and use of a discovery template in the form of a systems ontology to help reduce experimental trial and error, and eventually to accelerate discovery. A discovery template could assist

scientists in their quest to formulate gestalt or holistic patterns needed to see the big picture in each endeavor.

Chapter 5: Summary and Conclusion

REVIEW OF PREVIOUS CHAPTERS

The key findings of this investigation are that (1) Nobel Laureate research patterns can be mapped onto a General Systems Theory ontology that represents matter-energy and information processing at the cellular, organ and organism levels of analysis (Appendix C). In a reverse fashion, a General Systems ontology can be mapped onto the discovery patterns of Nobel Laureates analyzed; (2) a systems template could be developed to provide information seeking and ordering heuristics, or rules of thumb, to prompt the discovery process as well as to explain better past discoveries; (3) a large sample of 62 Laureate accounts reveals that they contain an average of very close to seven sections. This number is remarkably close to the classical "seven plus or minus two" limits of human short-term memory. Laureate discoveries consist of conceptual system representations that contain about seven plus or minus two ordered subsystem representations, that is, cognitive chunks.

The investigation involved the scrutiny of numerous Nobel Laureate autobiographical accounts of discoveries in order to discern overall discovery and information use patterns in medicine and physiology. Chapter 1 provides an overview of learning from the scientific discovery process and information use patterns. The first chapter also makes a case for using Nobel Laureate autobiographical accounts as primary data, and proposes use of content and critical incident analysis as key exploratory methods. The first hypothesis of the study is that Laureate discovery patterns in physiology or medicine are characterized by the gradual acquisition of a critical but unorganized mass of knowledge that, upon being ordered and synthesized, produces the discovery. Discovery outcomes tend to consist of about seven basic components, which

appears to reflect more than limited human short-term memory. The second hypothesis proposes that critical research incidents serve to direct, redirect or culminate research efforts. Critical incidents consist of such events as the formation of creative insights, research impasses that arrest progress, or serendipitous events that redirect researchers. The third hypothesis proposes that Laureates who completed medical education tend to deploy their clinical problem-solving patterns in scientific research. The exploration of discovery and information seeking patterns among Nobel Laureates can produce insights that serve to guide future scientific research and the design of systems to support fundamental research.

Chapter 2 reports on a pilot exploration that attempts to discern basic discovery and information use patterns within and among 20 Laureate autobiographical accounts. As stated above, a key insight that emerges from this analysis, as well as those that follow, is that all of the scientists tend strongly to employ a systems paradigm in their research pursuits. The discoveries themselves consist of systematic conceptual representations of normal or pathological physiological and anatomical processes, which occur within or among cells, organs or organisms. The key benefit of this chapter's pilot analysis is that it reveals the clear dominance of systems thinking among the Laureates in their information seeking and quest for understanding basic biological phenomena, including disease. The chapter's analysis also reveals that the second hypothesis is not well supported. Critical research incidents were not highly instrumental in directing or redirecting Laureate research. Instead, it was found that Laureates tend to pursue their investigations with zealous and persistent dedication, successive trial and error experimentation, and relentless and thorough replication of results. Obviously, critical incidents do come into play in their research, as in the case of Fleming's accidental discovery of penicillin, but these critical events appeared to play a minor role throughout

the other pilot cases analyzed. The third hypothesis, that physicians deploy their clinical problem solving techniques in their research investigations is adjudged to be partially true. First and foremost, Laureates are scientists and researchers; secondarily, they are clinicians.

In summary, Chapter 2's exploration brought out the importance of systems modeling to this investigator, thus confirming the paramount importance of the first hypothesis, and played down the importance of both the second (critical incident) hypothesis and the third (clinical heuristics) hypothesis. This does not mean that the second and third hypotheses are untrue or that these hypotheses would not produce insights in the framework of different investigations of research patterns. The second and third hypotheses were deemed to be less fruitful in the present investigation and were thus not directly further pursued in order to concentrate on the more revealing systems model. The pilot analysis served to direct and delimit this investigation to a further exploration of mental systems modeling view of each Laureate's discovery and information seeking processes.

Chapter 3 involves a more concentrated analysis of a systems model of discovery through reanalysis of Chapter 2's pilot cases. In each of 20 cases it can be seen that Nobel Laureates possess a keen ability to analyze phenomena and synthesize experimental findings through the use of highly systematic conceptual models. Each model consists of about seven subsystem components. These subsystem components are embedded in each Laureate's discovery account, particularly in the subdivision of their speeches into seven or so sections. That is, each discovery outcome represents a holistic and abstract systems view of an aggregate of something like five to nine interactive cellular, organ or organism subsystems. In turn, Laureates appear to fuse together each subsystem from sub-subsystem building blocks. The Laureates were meticulous in exploring the details

necessary to depict accurately the fundamental processes within each building block, as they engaged in systems building from the ground up. Thus, Chapter 3 serves the function of further confirming the systems hypothesis of discovery, and calls forth the necessity of using General Systems Theory. Conveniently, in the 1995 paperback edition of his book *Living Systems*, J. G. Miller provides a masterful synthesis of General Systems Theory. It was somewhat of a serendipitous discovery on the part of this investigator that Miller's systems ontology appears to match and explain the underlying dynamics of Laureate discovery mechanisms and systems. This insight led the investigator to employ a formal systems ontology in the next chapter's analysis.

Chapter 4 presents two formal General Systems ontologies, each represented as a matrix (see Appendix C). The first matrix includes eight levels of analysis on the left-side column (including three used in this analysis: the cellular, organ and organism levels) and eight cells across the top to depict the subsystems which process matter-energy (ingestor, distributor, converter, producer, storage, extruder, motor, supporter). The second systems ontology matrix also includes the cellular, organ and organism levels of analysis on the left side (among others), and ten subsystem cells which process information across the top (input transducer, internal transducer, channel and net, timer, decoder, associator, memory, decider, encoder, output transducer). In this study, these ontologies serve to explain and rationalize the matter-energy and/or information processing patterns discovered and depicted by Nobel Laureates at the cellular, organ and organism levels of analysis. The functional components of each Laureate's discovery account can be mapped onto the systems ontology as illustrated in this chapter's analysis. In a reverse fashion, the systems ontology could in the future be productively embedded into fundamental research processes to guide and prompt discovery. This chapter also reveals through a statistical analysis (t-test, mean, median, standard deviation, average deviation)

of 62 cases that Laureates tend to illustrate their discoveries with an average of seven subsystem processes or components. These seven components match fairly closely to the eight subsystem components in Miller's matter-energy ontology and to the 10 in his information processing subsystems ontology. The limited number of subsystem components represented in both the systems ontologies and each Laureate's account appears to reflect limited human short-term memory capacity. That is, humans can process only a few cognitive chunks at a time within their working, short-term memories. In the case of research activities, which are recorded and conducted through extended time periods, it appears that G. A. Miller's (1956) classical "Seven Plus or Minus Two" chunks can be processed in working memory at a given time. Moreover, there appears to be a continuum of processes carried out between human short- and long-term memories. In short, Laureate research patterns consist of about seven subsystem chunks or components, while J. G. Miller's General Systems ontologies encompass 8 to 10 subsystem categories. In conclusion, General Systems ontologies served well as templates to categorize the subsystem processes and entities represented in each Laureate's account. The template could be adapted and deployed to support future research and discovery efforts.

IMPLICATIONS

By now General Systems Theory is reasonably well developed and possesses great potential to aid in the understanding and formalization of the dynamics of fundamental research processes that lead to discovery breakthroughs. J. G. Miller, M.D., Ph.D., was educated as a physician and as a research scientist. In particular, his synthesis of General Systems Theory appears to be highly applicable to the task of understanding Laureate research, information seeking and discovery patterns. This investigation attempts to couple subsystems ontologies from General Systems Theory with subsystem

components represented within each Nobel Laureate's account of his or her scientific breakthrough. This investigation has been successful in mapping Laureate subsystems onto Miller's systems ontology, and conversely. One of the major potential contributions of this investigation is to provide a rudimentary understanding of the underlying systems dynamics inherent in Nobel Laureate research. Systems ontologies could be developed into "discovery templates" to guide fundamental research, to reduce experimental trial-and-error, and to accelerate the discovery process.

In ancient times, it required something like 300 years to produce a discovery synthesis (e.g., Euclidian geometry, 600 to 300 B.C.). For Newton to make his discovery of calculus in 1666, he needed to synthesize 93 years of the mathematical concepts of his forerunners. To formulate his concept of universal gravitation, Newton combined concepts of his predecessor scientists from 1543 (Copernicus) to 1687 (Newton, *Principia)*, a span of 144 years (G. Harmon, 1973, pp. 22-28). The Laureate cases reviewed in this investigation generally required a synthesis of findings from previous investigations that were made over a time period of two or three decades, plus each Laureate's synthesis of his or her own findings. Conceivably, the discovery process could be systematically performed so that the required time period to produce a breakthrough could be compressed to 10 or even five years, and eventually to one year. This time compression effort would likely call for the development and use of advanced search engine technologies based at least partially on systems ontologies.

The discovery process itself is being investigated in several areas: by artificial intelligence investigators; Nobel Laureate biographers; history of science scholars; and information scientists who study information seeking, needs, and behavior. Herbert A. Simon, for example, attempted to formalize a theory of scientific discovery in his *Models of Discovery* (1977). Simon's overall contributions are summarized in *Models of a Man;*

Essays in Memory of Herbert Simon (Augier & March, 2004), which reveals how Simon developed discovery heuristics and simulations through his efforts in artificial intelligence. Nobel Laureate Michael Bishop (who was awarded the Prize in 1989 with Harold Varmus for their discovery that normal genes can be instrumental in causing cancer) revealed the deeper dynamics of persistent and sustained research at the cellular level in his *How to Win a Nobel Prize* (2003). Information scientist Donald O. Case has produced a rigorous synthesis of over four decades of research findings in his *Looking for Information; a Survey of Research on information Seeking, Needs, and Behavior* (2002). Baldwin and Hallmark (2001) provided detailed accounts of how various laboratory and field scientists explore topics in their research domains. It would seem likely that the cumulative results of these investigators will, in the near future, converge to shed light on the discovery process and serve to bring about a dramatic reduction of time required to produce a discovery.

Sixty-two cases are analyzed in Chapter 4 to discern the number of sectional representations in each Laureate's autobiographical account. The fact that Laureates tend to use an average of about seven sections (illustrated statistically at the 95% level of confidence) is significant from the standpoint of modeling and predicting fundamental discoveries (Goffman & Harmon, 1971; G. Harmon, 1973). The correspondingly limited number of subsystems represented in the General Systems ontology matrices also seems to parallel the Laureates' numerical limits. The fact that both sets of representations are limited demonstrates the apparent operation of human short-term memory limits. Obviously, other factors than human short-term (working) memory can contribute to the use of a small number of sections, about seven, in Nobel Laureate reports. For example, by using a smaller number of sections, scientists make the complexities of their research more understandable to their readers, and make their own reporting shorter and easier.

Writing protocols in all languages and fields demand some degree of brevity. Nevertheless, extensive research findings in psychology converge on short-term memory limitations as the key set of limiting factors. Short-term memory appears to impose severe constraints both on human analytical reasoning and human reporting. Related current debates among psychologists, in fact, do not center on whether or not short-term memory serves as a major factor, as it clearly does. Instead, current psychological discussions debate the numerical span of short-term memory under different conditions, and also introduce other influences, such as the interactions between long- and short-term memory, or the kinds of concepts that come into play (Baddeley, 1994; Medin et al., 2000).

Therefore, the systems components of the discovery process, along with the severe numerical limitations imposed by human working memory, can guide the development and deployment of future search and research engines. Conceivably, each inquiry devoted to subsystem and sub-subsystem analysis could be supported by highly targeted search engine retrieval. Search engines could be customized to support fundamental experimental research at the cellular, organ and organism levels. This investigation might serve to demonstrate that Nobel Laureate research, information seeking and discovery patterns suggest that a far different thrust is needed in information retrieval research. Future retrieval systems, instead of being based on question-and-answer, Boolean search strategies, might better be based on the highly systematic block building and inductive approaches that most Laureates used. The Laureates studied in this investigation eventually produced gestalt or holistic conceptual systems, (pictures of normal and abnormal physiological processes) which themselves constituted discoveries. That is, Laureates tended to synthesize massive amounts of experimental findings and to organize their findings into successively higher systems levels until the big picture was

drawn and then meticulously verified. Their efforts stand in stark contrast to less productive reductionistic research approaches.

LIMITATIONS OF THIS INVESTIGATION

A *first* limitation of this research centers on its restricted sampling of the total set of over 100 years of Nobel Laureate accounts. Because the number of Laureate autobiographical accounts in physiology or medicine is now approaching 200 cases, there is a broad range of cases from which to sample. Initially, the investigator sought very ambitiously to analyze nearly all the available Laureate accounts. This ambition was based on the very naïve assumption that each case analysis would only require about four hours and that Laureate research patterns would be more readily apparent. As research progressed, it was noted that each case could easily require one to several days of analysis to understand its content, the writing nuances of its author, and, most importantly, to discern the underlying dynamics of each discovery process. The more that one reads, analyzes and reflects on any given case, the more that new insights, subtle differences and other lessons emerge about discovery from the rich tapestry of that case. Thus, there exists a clear tradeoff between sampling breadth and depth. If an observer thinks that all has been gained that can be gained from a case with one or two readings, that observer might well think again, and reread another time or two. Here, the law of diminishing returns does not seem to apply very well. Subsequent re-readings seem to bear more fruit than initial readings.

Further, there exists such a broad variety of cases and a multiplicity of ways in which these cases can be classified and subsequently sampled: by subject; by various time spans; according to geographical and nationality criteria; according to Laureate presentation styles (sectioning, illustrations, formalizations, citation styles); by research approach, such as laboratory experimentation or field research; by use of inductive or

deductive logic; and so on. The sampling of cases to analyze is a much more complex problem than most casual observers might realize. Accordingly, the next section, which contains suggestions for future research, deals more extensively with case sampling problems.

A *second* key limitation of this study is the investigator's lack of formal education in the life and physical sciences. As a history major and librarian, the investigator has through the years developed an interest in the history of science, and was therefore attracted to this topic. But the lack of in-depth knowledge about physiology, medicine and biochemistry hindered analysis throughout. The primary dissertation advisor, possessing more knowledge of the sciences and discovery processes, helped to interpret various cases and to discern their implicit discovery patterns. The next section concerning suggestions for future research, briefly discusses the need for expertise in analyzing Laureate cases and the potential use of expert or knowledge-based systems.

A *third* limitation is that the analysis of each case is inevitably a subjective endeavor as well as an objective task. Each observer will most likely provide his or her own interpretation of each Laureate's account, and provide different perspectives that might prove to be profitable for different analytical purposes. Many of the interpretations of the cases analyzed here, are the joint product of this investigator and her key advisor, since this work was to some degree a joint research effort. Again, the next section on future research suggests ways to enhance scientific validity and reliability in the analysis of Laureate cases.

A *fourth* limitation is that the application of General Systems ontologies to categorize parts of different Laureate discovery representations is likewise subject to subjective judgment, in addition to being an objective task. The systems ontology investigator must select different subsystem representations from each Laureate's written

account and "plug" them into the systems ontology subsystems categories. This limitation was somewhat compensated by the incorporation of J. G. Miller's own analysis of a few Laureate discoveries in his book *Living Systems*. For example, Miller provided his own analysis of cardiac functioning, using systems ontology subsystem categorizations. Miller's analysis helped this investigator to translate Einthoven's 1924 account into subsystem terminology compatible with the systems ontology. Ontology categorization limitations are discussed further in the next section.

The above list of limitations is not exhaustive and, no doubt, other limitations of this study exist. The next section on Future Research Directions attempts to address some of these limitations by providing suggestions for future researchers who address discovery and information use patterns of Nobel Laureates.

FUTURE RESEARCH DIRECTIONS

This section suggests some possible future research directions that Nobel Laureate investigators might wish to consider in their quest to understand information use and discovery patterns of Nobel Laureates in Physiology or Medicine and, by extension, in other Nobel Prize areas—chemistry and physics.

A *first* possible future research direction is for researchers to concentrate on the study of Laureate autobiographical accounts, since they serve as exemplars of scientific research, and particularly to explore the dynamics of information use and discovery. Nobel cases provide an extremely rich repository of lessons for historians, philosophers, and sociologists of science; information scientists; medical researchers; science students at all levels of education; artificial intelligence specialists; statisticians; students of research methodology; and others. This is not to say that the selection of Nobel Laureate recipients is not to some degree biased or politicized. Nevertheless, this investigator continues to be perplexed about why researchers apparently do not draw more upon this

rich repository of research experiences. Although it is hard work, the gold is there to mine.

A *second* possible future research direction is to consider very carefully the different ways to sample the abundance of Laureate accounts now available. These sampling considerations are treated at length and thus listed in order.

(1) The Nobel awards in this study cover a time period of nearly nine decades, from 1901–1990. Throughout this time span, the topical themes of investigation evolved from early preoccupations such as those associated with communicable diseases and rudimentary analyses of anatomical and physiological processes. Then in the 1930s and 1940s, attention turned largely to nutritional and antibiotic investigations. In recent decades, there has been an emphasis on cellular phenomena, including cancer and DNA synthesis. Thus, there appears to be a different zeitgeist or spirit of the times that drives research agendas during successive decades (Feldman, 2000; Harittai, 2002; Lindsten & Ringertz, 2001; Raju, 2002; Shalev, 2002), with the result that Laureate discovery and information use patterns evolve and change accordingly. Furthermore, communications between different scientists evolved over the course of the century: the production and distribution of publications became more widespread and faster; the telephone and television came into use; modes of travel improved in terms of speed, convenience and economy. Scientific endeavor became more of a global phenomenon and there was a big growth in scientific specializations with a corresponding change from little science to big science. Major changes like these have altered the nature of discovery and information use patterns among the Nobel Laureates in Physiology or Medicine. Each time frame can produce its own mode of investigation and condition its topical thrust.

(2) Also with regard to sampling, the Nobel discoveries were made in many different countries and by scientists who used different languages including German,

English, Danish, Russian, Swedish, French, Flemish, and Hungarian, among others. There is a heavy representation of Occidental scientists among the Nobel Laureates. Such cultural, linguistic and geographical factors can influence patterns of discovery and information use, and also impact the sampling and analysis of Laureate cases.

(3) A third sampling consideration for selection of Laureate awards in Physiology or Medicine for analysis is that these awards have been given for a highly diverse set of topics:

- to confront communicable diseases such as diphtheria, malaria, tuberculosis, yellow fever, typhus, and polio, with a focus on immunology and utilization of vaccines and insecticides;
- to identify the epidemiology, pathogenesis, diagnosis, treatment, and prognosis of different persistent diseases, such as cancer, diabetes, nervous system disorders (including eye and ear neural mechanisms), anemia, cardiovascular and heart disease;
- the physiology and biochemistry of various regulatory mechanisms and dynamics of molecular, organ, and organismic systems, including Cajal and Golgi bodies, the regulation of blood flow, the production of enzymes, nervous system control, and DNA/RNA functionality;
- surgical interventions, such as organ and bone marrow transplantation and neurosurgery;
- the discovery of effective drugs, such as penicillin and streptomycin;
- the discovery of specific metabolic dynamics and nutritional factors, such as the impact of vitamins C and K, glucose metabolism in diabetes, protein and carbohydrate utilization, and cholesterol production;

- the invention of diagnostic and treatment instruments, such as the electrocardiogram machine, computer axial tomography, and radiation therapy systems;
- the cellular, genetic and microbiological basis of oncogenesis and cancer, including DNA alteration and mutation, RNA transfer, and retrovirus influences;
- the identification of biochemical, physiological and anatomical entities and features, such as the citric acid cycle, different human blood groups and neural fibers and structures.

While the above typology of Nobel discoveries is not exhaustive, it does represent the broad range of topics available for exploration in any study. Different investigative approaches and discovery dynamics are at work in the above research categories. Discoveries in biochemistry appear to be different from discoveries of new surgical interventions or diagnostic instruments. The discovery and information use patterns of these diverse sets of Nobel Laureates are also correspondingly diverse. In research efforts, common patterns could be more apparent within homologous groups of Nobel Laureates than among heterogeneous groups. Even then, the problem of sampling from this large population subset continues to be complex.

(4.) A fourth sampling consideration arises from the different research approaches and modes that Nobel Laureates have employed. Some were independent scholars or intellectual foot soldiers, and this was especially true during the first four decades of the twentieth century. From about 1940, research teamwork and collaboration appeared to characterize most of the efforts, and often there were co-recipients for each year's award. Sometimes the parallel (same year) award cases each made up a part of a larger picture or puzzle. At other times, such co-recipient awards related to different topics. Furthermore,

some discoveries were characterized by a serendipitous event, such as Fleming's discovery of penicillin, while other discoveries were characterized by slow, methodical laboratory work over successive decades, such as Barbara McClintock's discovery about genome response to challenge. Other Laureates conducted field observations of human or animal communities and their conclusions were founded on systematic reviews of these field observations. In such heterogeneous research thrusts, discovery and information use patterns can vary widely and common themes can be harder to detect.

(5.) A fifth sampling consideration is that different Laureates address problems associated with different systems levels: molecular, cellular, tissue, organ, organism, or community levels. DNA investigations, for example, differed from those focusing on more general viral or bacterial phenomena. The study of community disease patterns calls for the gathering of bio-statistical data and the observation of epidemiological patterns. Successful organ transplantation required successive trial-and-error experiments on laboratory animals. Thus, patterns of studies at the micro-systems level can vary considerably from those at intermediate or macro-systems levels. Additionally, different investigators addressed different General Systems components. These components include organs and physiological processes involved with the input, throughput or output of various kinds of energy, information or material. Different internal regulatory, associative or transduction mechanisms were the object of study. Collectively, these different systems approaches can serve as different bases for selecting which discoveries to study from among the population of Nobel Laureate discoveries in medicine and physiology.

The above list of five sampling considerations is not exhaustive nor are the different sampling approaches mutually exclusive. The study of discovery patterns among the large group of Nobel Laureates in Physiology or Medicine can obviously be

approached from many different vantage points, depending on one's purposes, hypotheses and sampling preferences. Each approach can be more or less revealing or fruitful. Specifically focused studies of Nobel Laureate discovery patterns might produce more insight than general approaches. One might specialize by studying discovery patterns of researchers who address specific diseases or syndromes, or particular biochemical, neurological or microbiological processes. Different time periods and patterns might be studied, as might comparisons of discoveries that emerged from different countries. The influence of critical incidents, clinical problem-solving heuristics and bibliometric citation patterns could all be examined. There are virtually innumerable approaches to investigating discovery and information use patterns among these leading researchers.

A *third* possible research direction is to incorporate human or artificial intelligence expertise into research on Nobel Laureate discovery patterns. The investigator's lack of scientific and medical expertise was one of the continual challenges throughout this dissertation investigation. In the last four decades, there has been considerable progress in the area of general problem solving and expert system development, and there exists an impressive body of accumulated knowledge on the topic of "expertise" itself. Ericsson and Smith (1991), summarize some of this knowledge and stress the point that expert performance is primarily a function of acquired skill that derives from the accumulation of domain or subject-specific knowledge and methodology throughout many years of education and practice. The more recent study of expertise has been directed to the characteristics of scientists or professionals who specialized in specific domains, rather than to the study of generalists. Impressive developments in the area of knowledge-based systems (a more recent term often used to represent expert systems) have been recorded (Stefik, 1995). A researcher could indeed become an expert

in the study of Nobel Laureate awards in the sub-areas of medicine or physiology, such as DNA alteration or RNA transfer. In a similar manner, domain specific expert or knowledge-based systems could be targeted to support the analysis of their corresponding Laureate domains or sub-domains. The methodological expertise possessed by Laureates should be a fruitful area of research to reveal precisely how domain experts function in their specialized research environments. Last, case-based reasoning, another artificial intelligence technique, could be applied to indexing common features among Laureate cases (Leake, 1996).

A *fourth* suggestion for future research stems from the need to reduce observer bias in the study of Nobel Laureate cases. This might be done by directly quoting key points in each Laureate's account. While it may be true the Laureates have a tendency to be more or less accurate in recounting their own research stories, at least their accounts come from their own memories and appear to be reasonably dependable as primary evidence. In contrast, when an outside observer attempts to paraphrase or interpret Laureate accounts, it is likely that observer bias can be introduced. Alternatively, a student of Laureate discoveries might rely on the presentation speeches that precede each year's lectures and summarize their content. These presentation speeches are delivered by distinguished scientists and appear to provide elegant, simplified, accurate summaries. Future researchers might well exploit these presentation speech summaries and the quoted remarks of Laureates to obtain accurate and telling content and reveal underlying patterns

A *fifth* suggestion for future research on information use and discovery patterns involves the further use and exploitation of General Systems Theory subsystem ontologies (Appendix C). The key elements of Laureate accounts can be fruitfully categorized and placed into these subsystem categories. This investigator was impressed

by the extent to which Laureate-derived conceptual systems and subsystems were so commensurable with the ontology subsystems, and how they could be so conveniently mapped thereon. The ontology systems categories could be further developed to include not only subsystems, but also sub-subsystems, sub-sub-subsystems, and so on. A more elaborate and subdivided set of General Systems ontologies could be developed and applied to specialized domains of Laureate inquiry in medicine and physiology, and most likely in chemistry and physics as well. Further, researchers could profitably rely on what is by now a reasonably well-developed field of General Systems Theory. Some General Systems literature incorporates Laureate discoveries into discussions of how natural systems can be addressed at different levels. Systems interpretations can suggest ways to interpret research findings and explain the dynamics of recorded discoveries. J. G. Miller, in his masterful work, *Living Systems* (1995) discussed a limited number of systems facets of several Laureates in Physiology or Medicine. These Laureates include the following scientists: Adrian, Beadle, Crick, Eccles, Edelman, Erlanger, Gasser, Granit, Hartline, Holley, Hubel, Jacob, Kandel, Katz, Lipmann, Lorenz, Medawar, Monod, Nirenberg, Pallade, Pavlov, Sherrington, Sperry, Tinbergen, Wald, Watson, and Wiesel. Even though Miller's discussion of the above scientists is scattered and limited, this investigator found his analysis of Laureate conceptual systems to be useful in understanding overall systems relationships. J. G. Miller's analyses of these Laureates' work can also be used to reduce observer bias among systems-oriented investigators who study Laureate researchers.

A *sixth* direction for future research is to formalize the discovery process mathematically. Mathematical symbolizations are abstract and lend themselves to manipulation, statistical analysis, and computation. Goffman and Harmon (1971) used Harmon's set theory model to explain the cognitive dynamics of the discovery process. A

discovery outcome consists of a *complete*, *ordered* set of cognitive elements: {*a, b, c, d, e, f, g*}. That is, the discoverer arranges a complete group of cognitive chunks into an ordered set to represent his or her discovery in terms that reflect human short-term memory limitations (seven plus or minus two chunks). In order to get to this final discovery outcome (which is characterized as Stage IV in the discovery process, where there is a sufficient number of chunks and these chunks are properly organized), the researcher must go through Stages I, II, and III. Stage I, at the outset of inquiry, consists of an empty or null set: { }; that is, there is *insufficient* information and *none to order*. For example, a scientist might attack a problem about which little is known and the problem itself is poorly defined. Thus, few concepts or chunks exist at the outset of inquiry and there are few or no chunks to organize. Stage II, *insufficient* but *ordered* information, occurs when the scientist tentatively designates several information elements or chunks as relevant to the inquiry. The number of elements is sufficient to establish set ordering relations and to imply the bounds of a cognitive set: {*a,…d, e, g*}. The scientist's task here is to order the available information and to discern what else needs to be known to fill in the gaps. Stage III, *sufficient* but *unordered* information, occurs when our researcher has acquired a sufficient number or even a surplus of information elements: {*a, x, f, c, d, e, b, g, k*}. At this stage, the scientist might undergo information overload; that is, the limits of human short-term working memory have been exceeded and ordering problems further confound inquiry. It is particularly at this point that systems ontologies can be helpful to order the various chunks (or Laureate sections, for example) through the use of a subsystems template. The scientist must weed out irrelevant chunks and order the remaining relevant chunks. Finally at Stage IV, the scientist arrives at a *sufficien*t and *ordered* information set: {*a, b, c, d, e, f, g*} and this completes the research task and constitutes a discovery. Elements *k* and *x* have been

deleted from the discovery set as essentially irrelevant chunks. Overall then, the discovery process might well be regarded as a dynamic, iterative and trial-and-error process in which cognitive chunks are obtained and permuted until a complete, ordered discovery set is obtained and verified. The dynamics of this set model were somewhat apparent in the latter stages of this investigation. J. G. Miller's subsystems ontology (at either the matter-energy or information processing system representations of the cellular, organ, or organism levels) can be used to encompass a *sufficient* and *ordered* set of information elements—a discovery set. In all cases analyzed in this investigation, the discovery set and the systems template appear to be circumscribed according to the limitations of human short-term memory.

A *seventh* possible direction for future research is to combine the study of Nobel discovery patterns with the capabilities of emerging search and research engines. There have been some recent, impressive advances in research engine design to help researchers frame problems and retrieve highly relevant, directly usable information. The General Systems templates utilized in this investigation definitely helped this investigator to better understand the various Laureate cases analyzed. These systems templates could be more elaborately developed to frame specialized kinds of subsystem and sub-subsystem biological phenomena at the cellular, organ and organism levels. Further, the system templates could be applied in fundamental research to work as discovery templates to guide or even accelerate research efforts. Last, systems templates could be incorporated into research engines to support research at all system levels. Already, for example, the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/) has developed an impressive array of bioinformatics databases and the *Enterez* retrieval system to support research in molecular biology and computation. Other retrieval aids, such as the National Library of Medicine's *Medical Subject Headings* (2005), help

researchers to convert search terms automatically into controlled vocabulary and map the terms into useful hierarchies. Various bioinformatics or biomedical representations might in the future be augmented through the use of systems template ontologies.

CONCLUSION

Chapter 1 explains the purpose and approach of this study. Chapter 2 reports the results of a pilot analysis of basic discovery patterns. Chapter 3 extends the pilot analysis to confirm the usefulness of a systems model of discovery. Chapter 4 discusses how a General Systems ontology can be used to both explain and facilitate scientific discovery in medicine and physiology. This fifth chapter provides an overall summary of the investigation, discusses implications and the investigation's limitations, and proposes future research directions.

The overall implications of this investigation are that General Systems Theory ontologies can be useful in explaining and facilitating Nobel Laureate discovery and, potentially, to support or accelerate the discovery process. There appears to be a convergence of findings from information need and use studies, artificial intelligence, histories of Laureate discoveries, and other fields, to help explain and formalize an incipient science of discovery.

While this investigation was somewhat handicapped by various limitations (restricted sampling, the investigator's lack of scientific education, and the subjective nature of analysis of Laureate cases and mapping data to systems ontologies), seven potentially fruitful directions for future research emerged. First, Nobel Laureate accounts are literal gold mines of information about the discovery process and should be studied more fully. Second, given the large number of Laureate cases now available, it is desirable to address very carefully the sampling problems that inevitably arise in selecting cases to analyze. Third, human or artificial intelligence domain expertise might

well be applied in future studies of Laureate discoveries. Fourth, observer bias in the study of Laureate cases can be reduced through the use of Laureate quotations and excerpts from the presentation speeches that accompany each year's Laureate addresses. Fifth, the General Systems Theory ontology can be highly useful in the analysis of cases and potentially could serve as a discovery template. Sixth, the discovery process itself needs to be further formalized through the use of mathematical representations. Seventh, and last, future research engine development might well incorporate systems ontologies to facilitate and catalyze the discovery process. Ultimately, search engine design might be based on formalizations gleaned from the study of discovery patterns, among other factors.

Finally, in closing, it is perhaps appropriate to mention that James G. Miller, in developing his landmark treatise on *Living Systems*, noted that he was driven by the aims of the Harvard Society of Fellows, which he joined in 1938:

> You will seek not a near, but a distant, objective, and you will not be satisfied with what you may have done. All that you may achieve or discover you will regard as a fragment of a larger pattern, which from his separate approach every true scholar is striving to descry (1995, p. xxiv).

Because this quotation seems to epitomize the drive and spirit of the Nobel Laureates in this study, these Laureates would probably have been proud to include James G. Miller in their numbers.

Appendix A: Nobel Laureates in Physiology or Medicine, 1901-1990

Year	*Nobel Laureates*	
1901	Emil Adolph von Behring	
1902	Ronald Ross	
1903	Niels Ryberg Finsen	
1904	Ivan Petrovich Pavlov	
1905	Robert Koch	
1906	Camillo Golgi	Santiago Ramón y Cajal
1907	Charles Louis Alphonse Laveran	
1908	Eli Metchnikoff	Paul Ehrlich
1909	Emil Theodor Kocher	
1910	Albrecht Kossel	
1911	Allvar Gullstrand	
1912	Alexis Carrel	
1913	Charles Robert Richet	
1914	Robert Bárány	
1915	not awarded	
1916	not awarded	
1917	not awarded	
1918	not awarded	
1919	Jules Bordet	
1920	August Krogh	
1921	not awarded	
1922	Archibald Vivian Hill	Otto Fritz Meyerhof
1923	Frederick Grant Banting	John James Richard Macleod
1924	Willem Einthoven	
1925	not awarded	
1926	Johannes Andreas Grib Fibiger	

1927	Julius Wagner-Jauregg		
1928	Charles Jules Henri Nicolle		
1929	Christiaan Eijkman	Frederick Gowland Hopkins	
1930	Karl Landsteiner		
1931	Otto Heinrich Warburg		
1932	Charles Scott Sherrington	Edgar Douglas Adrian	
1933	Thomas Hunt Morgan		
1934	George Hoyt Whipple	George Richards Minot	William Parry Murphy
1935	Hans Spemann		
1936	Henry Hallett Dale	Otto Loewi	
1937	Albert von Szent-Györgyi Nagyrapolt		
1938	Corneille Jean Francois Heymans		
1939	Gerhard Johannes Paul Domagk		
1940	not awarded		
1941	not awarded		
1942	not awarded		
1943	Henrik Dam	Edward Adelbert Doisy	
1944	Joseph Erlanger	Herbert Spencer Gasser	
1945	Alexander Fleming	Ernst Boris Chain	Howard Walter Florey
1946	Hermann Joseph Muller		
1947	Carl Ferdinand Cori	Gerty Theresa Cori-Radnitz	Bernardo Alberto Houssay
1948	Paul Hermann Müller		

1949	Walter Rudolf Hess	António Caetano de Abreu Freire Egas Moniz	
1950	Edward Calvin Kendall	Tadeus Reichstein	Philip Showalter Hench
1951	Max Theiler		
1952	Selman Abraham Waksman		
1953	Hans Adolf Krebs	Fritz Albert Lipmann	
1954	John Franklin Enders	Thomas Huckle Weller	Frederick Chapman Robbins
1955	Axel Hugo Theodor Theorell		
1956	Andre Frederic Cournand	Werner Theodor Otto Forssmann	Dickinson Woodruff Richards, Jr.
1957	Daniel Bovet		
1958	George Wells Beadle	Edward Lawrie Tatum	Joshua Lederberg
1959	Severo Ochoa	Arthur Kornberg	
1960	Frank Macfarlane Burnet	Peter Brian Medawar	
1961	Georg von Békésy		
1962	Francis Harry Compton Crick	James Dewey Watson	Maurice Hugh Frederick Wilkins
1963	John Carew Eccles	Alan Lloyd Hodgkin	Andrew Fielding Huxley
1964	Konrad Bloch	Feodor Lynen	
1965	Francois Jacob	Andre Lwolff	Jacques Monod
1966	Peyton Rous	Charles Brenton Huggins	
1967	Ragnar Granit	Haldan Keffer Hartline	George Wald
1968	Robert W. Holley	Har Gobind Khorana	Marshall Warren Nirenberg
1969	Max Delbrück	Alfred Day Hershey	Salvador Edward Luria
1970	Julius Axelrod	Ulf S. von Euler	Bernhard Katz
1971	Earl W. Sutherland		
1972	Gerald M. Edelman	Rodney R. Porter	
1973	Karl von Frisch	Konrad Lorenz	Nikolaas Tinbergen

1974	Albert Claude	Christian de Duve	George E. Palade
1975	David Baltimore	Renato Dulbecco	Howard M. Temin
1976	Baruch S. Blumberg	D. Carleton Gajdusek	
1977	Roger Guillemin	Andrew V. Schally	Rosalyn S. Yalow
1978	Werner Arber	Daniel Nathans	Hamilton O. Smith
1979	Alan M. Cormack	Godfrey N. Hounsfield	
1980	Baruj Benacerraf	Jean Dausset	George D. Snell
1981	Roger W. Sperry	David H. Hubel	Torsten N. Wiesel
1982	Sune K. Bergström	Bengt I. Samuelsson	John R. Vane
1983	Barbara McClintock		
1984	Niels K. Jerne	Georges J. F. Köhler	Cesar Milstein
1985	Michael S. Brown	Joseph L. Goldstein	
1986	Stanley Cohen	Rita Levi-Montalcini	
1987	Susumu Tonegawa		
1988	James W. Black	Gertrude B. Elion	George H. Hitchings
1989	Harold E. Varmus	J. Michael Bishop	
1990	Joseph E. Murray	E. Donnall Thomas	

Appendix B: Content Analysis Categories

Critical Incident Events

Seminal research
Research initiation
Research acceleration
Research stoppage or impedance
Research redirection
Hypothesis formation
Notable quotations
Accidents
Surprises
Serendipitous encounters
Iconoclastic stances
Rationalistic thinking

Clinical Problem-Solving Heuristics

Diagnostic clusters of observation
Differential diagnosis
Proof by exclusion
Syndrome recognition
Pattern building
Intuitive hunches
Early hypothesis
Key clue
Lanthanic
Pattern recognition

Knowledge Synthesis Events

Informal textual citations
Formal citations
Publication efforts
Self-citations
Explicit collaboration
Informal communications

General Systems Ontology

See Appendix C

Appendix C: General Systems Ontology Worksheets

Table P-2 Selected Major Components of Each of the 20 Critical Subsystems at each of the Eight Levels of Living Systems (Part 1) from Miller, J.G. 1995, p. xx.

SUBSYSTEM LEVEL	**REPRODUCER**	**BOUNDARY**	**INGESTOR**	**DISTRIBUTOR**
CELL	Genes of parent cells	*Matter-energy and information*: plasma membrane	Coated pits	Microtubules and motor molecules
ORGAN	Upwardly dispersed to organism	Capsule or outer cell layer	Input artery	Intercellular fluid
ORGANISM	Testes, ovaries, uterus, genitalia	*Matter-energy and information*: skin or other outer covering	Mouth, nose, skin in some species	Vascular system of higher animals

Table P-2 Selected Major Components of Each of the 20 Critical Subsystems at each of the Eight Levels of Living Systems (Part 2) from Miller, J.G. 1995, p. xxi.

CONVERTER	**PRODUCER**	**MATTER-ENERGY STORAGE**	**EXTRUDER**	**MOTOR**	**SUPPORTER**
Enzymes that split molecules	Nucleus, ribosomes, endoplasmic reticulum	Triglyceride molecules in fat cells	Synaptic terminals of neurons	Cilia, flagellae, pseudopodia	Cytoskeleton
Upwardly dispersed to organism	Upwardly dispersed to organism	Central lumen of glands	Output vein	Smooth muscle, cardiac muscle	Stroma
Upper gastrointestinal tract	Organs that synthesize materials for metabolism and repair	Fatty tisues	Sweat glands of animal skin	Skeletal muscle of higher animals	Skeleton

Table P-2 Selected Major Components of Each of the 20 Critical Subsystems at each of the Eight Levels of Living Systems (Part 3) from Miller, J.G. 1995, p. xxii.

SUBSYSTEM LEVEL	**INPUT TRANSDUCER**	**INTERNAL TRANSDUCER**	**CHANNEL AND NET**	**TIMER**
CELL	Receptor site for hormone on plasma membrane	Cyclic AMP, Cyclic GMP	Openings through receptors on membranes	Oscillating biochemical process as in mitotic clock
ORGAN	Receptor cell of sense organ	Specialized cell of sinoatrial node of heart	Nerve net of organ	Heart pacemaker
ORGANISM	Sense organs	Sensory cells in organs	Blood vascular system, nervous system	Suprachiasmatic nuclei of hypothalamus

Table P-2 Selected Major Components of Each of the 20 Critical Subsystems at each of the Eight Levels of Living Systems (Part 4) from Miller, J.G. 1995, p. xxiii.

DECODER	**ASSOCIATOR**	**MEMORY**	**DECIDER**	**ENCODER**	**OUTPUT TRANSDUCER**
Molecular binding sites	Unknown	Unknown	Binding sites for information transmissions	Gene that specifies hormone	Presynaptic vesicles of neuron
Second echelon cell of sense organ	None found; upwardly dispersed to organism	None found; upwardly dispersed to organism	Sympathetic fibers of sinoatrial node of heart	Synthetic components of output neurons	Presynaptic region of output neuron
Sensory nuclei	Unknown neural components	Unknown neural components	Neural components at several echelons	Temporoparietal Area of dominant hemisphere of human cortex	Larynx

Appendix D: Section Counts from Published Nobel Laureate Lectures

To illustrate relations between short-term memory chunking and Laureate discovery components, this appendix displays the number of component sections from published Nobel lectures: Physiology or Medicine (1901-1990). The list of 62 Laureates presented below indicates the year of each award, the Laureate's last name, and the number of substantive sections in each Laureate's published lecture. Laureates who did not section off their published speeches or those who co-authored their lectures are not listed herein.

Year	Laureate	Sections
1931	Warburg	11
1933	Morgan	4
1944	Erlanger	7
1950	Reichstein	4
1950	Hench	4
1952	Waksman	11
1953	Krebs	8
1953	Lipmann	5
1955	Theorell	5
1957	Bovet	6
1958	Beadle	6
1959	Lederberg	7
1959	Ochoa	3
1959	Kornberg	9
1960	Burnet	3
1960	Medawar	6
1961	von Békésy	4
1962	Wilkins	11
1962	Watson	16
1963	Hodgkin	6
1963	Huxley	4
1964	Lynen	7
1965	Jacob	5
1965	Monod	5
1966	Huggins	7
1968	Holley	5
1968	Khorana	6
1968	Nirenberg	10

1969	Delbrück	6
1969	Hershey	2
1969	Luria	7
1970	Axelrod	10
1972	Edelman	6
1972	Porter	4
1973	Lorenz	7
1974	de Duve	5
1974	Palade	5
1975	Baltimore	5
1975	Dulbecco	7
1975	Temin	10
1976	Blumberg	10
1976	Gajdusek	10
1977	Schally	5
1978	Nathans	9
1978	Smith	9
1979	Hounsfield	10
1980	Dausset	5
1981	Sperry	7
1981	Hubel	7
1981	Wiesel	8
1982	Samuelsson	6
1983	McClintock	7
1984	Köhler	8
1984	Milstein	8
1986	Cohen	5
1986	Levi-Montalcini	11
1987	Tonegawa	14
1988	Black	3
1988	Elion	7
1989	Varmus	13
1989	Bishop	10
1990	Murray	9

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Vita

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